Chronic Inflammatory Disease

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO014

Description

The following biologics and biologic response modifiers are utilized in multiple chronic inflammatory disease states. Most of these agents target cytokines or other inflammatory mediators that are elevated in patients with such disease states. The purpose of this policy is to ensure the appropriate use of these agents.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Medications Included in this Policy

Indication	Medications
Ankylosing Spondylitis	• adalimumab (Humira®) • bimekizumab (Bimzelx®) • certolizumab (Cimzia®) • etanercept (Enbrel®) • golimumab (Simponi®/Simponi Aria®) • ixekizumab (Taltz®) • secukinumab (Cosentyx®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Adolescent Plaque Psoriasis	• ixekizumab (Taltz®)
Behcet Syndrome – ulcer of the mouth	• apremilast (Otezla®)
Crohn's Disease	• adalimumab (Humira®)

	• certolizumab (Cimzia®) • guselkumab (Tremfya®) • risankizumab (Skyrizi®) • ustekinumab (Stelara®) • vedolizumab SC (Entyvio®) • mirikizumab (Omvoh®) • infliximab-dyyb (Zymfentra®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi) • ustekinumab-auub (Wezlana) • ustekinumab-ttwe (Pyzchiva)
Cryopyrin-Associated Periodic Syndromes (CAPS) (including Chronic Infantile Neurological, Cutaneous and Articular Syndrome (CINCA) or Neonatal-Onset Multisystem Inflammatory Disease (NOMID))	• anakinra (Kineret®)
Cryopyrin-Associated Periodic Syndromes (CAPS) (including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS))	• rilonacept (Arcalyst®)
Enthesitis-Related Arthritis	• secukinumab (Cosentyx®)
Giant Cell Arteritis	• tocilizumab (Actemra®)

	• tocilizumab-aazg (Tyenne®)
Hidradenitis Suppurativa	• adalimumab (Humira®) • bimekizumab (Bimzelx®) • secukinumab (Cosentyx®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Non-radiographic Axial Spondyloarthritis	• bimekizumab (Bimzelx®) • certolizumab (Cimzia®) • ixekizumab (Taltz®) • secukinumab (Cosentyx®)
Polyarticular Juvenile Idiopathic Arthritis	• abatacept (Orencia®) • adalimumab (Humira®) • certolizumab (Cimzia®) • etanercept (Enbrel®) • sarilumab (Kevzara®) • tocilizumab (Actemra®) • tocilizumab-aazg (Tyenne®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®)

	• adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Psoriatic Arthritis	• abatacept (Orencia®) • adalimumab (Humira®) • apremilast (Otezla®) • bimekizumab (Bimzelx®) • certolizumab (Cimzia®) • etanercept (Enbrel®) • golimumab (Simponi®/Simponi Aria®) • guselkumab (Tremfya®) • ixekizumab (Taltz®) • risankizumab (Skyrizi®) • secukinumab (Cosentyx®) • ustekinumab (Stelara®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi) • ustekinumab-auub (Wezlana)

	• ustekinumab-ttwe (Pyzchiva)
Pediatric Crohn's Disease	• adalimumab (Humira®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Pediatric Ulcerative Colitis	• adalimumab (Humira®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Pediatric Plaque Psoriasis	• apremilast (Otezla®) • ustekinumab (Stelara®) • ustekinumab-auub (Wezlana) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek)

	• ustekinumab-aekn (Selarsdi) • ustekinumab-ttwe (Pyzchiva)
Pediatric Psoriatic Arthritis	• ustekinumab (Stelara®) • ustekinumab-auub (Wezlana) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) • ustekinumab-ttwe (Pyzchiva)
Plaque Psoriasis	• adalimumab (Humira®) • apremilast (Otezla®) • brodalumab (Siliq®) • bimekizumab (Bimzelx®) • certolizumab (Cimzia®) • etanercept (Enbrel®) • guselkumab (Tremfya®) • ixekizumab (Taltz®) • risankizumab (Skyrizi®) • secukinumab (Cosentyx®) • ustekinumab (Stelara®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi) • ustekinumab-auub (Wezlana) • ustekinumab-ttwe (Pyzchiva)

Polymyalgia Rheumatica	• sarilumab (Kevzara®)
Rheumatoid Arthritis	• abatacept (Orencia®) • adalimumab (Humira®) • anakinra (Kineret®) • certolizumab (Cimzia®) • etanercept (Enbrel®) • golimumab (Simponi®/Simponi Aria®) • sarilumab (Kevzara®) • tocilizumab (Actemra®) • tocilizumab-aazg (Tyenne®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Recurrent Pericarditis	• rilonacept (Arcalyst®)
Systemic Juvenile Idiopathic Arthritis	• anakinra (Kineret®) (Off Label) • tocilizumab (Actemra®) • tocilizumab-aazg (Tyenne®)
Systemic Sclerosis-Associated Interstitial Lung Disease	• tocilizumab (Actemra®) • tocilizumab-aazg (Tyenne®)
Ulcerative Colitis	• adalimumab (Humira®) • golimumab (Simponi®/Simponi Aria®) • guselkumab (Tremfya®) • risankizumab (Skyrizi®) • ustekinumab (Stelara®) • ozanimod (Zeposia®) • vedolizumab SC (Entyvio®) • mirikizumab (Omvoh®)

	• etrasimod (Velsipity™) • infliximab-dyyb (Zymfentra®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi) • ustekinumab-auub (Wezlana) • ustekinumab-ttwe (Pyzchiva)
Uveitis/Panuveitis	• adalimumab (Humira®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)

Applicable to All Disease States and Treatment Options Listed Below

I. Contraindication to one preferred treatment option listed in the policies below does not exempt the requirement to try another required agent prior to biologic approval. For instance, in the rheumatoid arthritis policy to follow, a contraindication to methotrexate but not to other available treatment options (sulfasalazine, hydroxychloroquine, leflunomide, etc.) would not satisfy criteria I(C)(1). In other words, a member would still need to try at least one of these other agents as clinically appropriate.

II. Approved treatments are not to be used in combination with other biologics or other non-biologic specialty medications used to treat autoimmune conditions. Use of TNF-alpha blockers such as adalimumab in combination with other biologics, such as anakinra or abatacept, has demonstrated and increased the risk of serious infection with insufficient evidence for added benefit. Per product labeling, use of concomitant biologics is not recommended as there is insufficient data to support this. Similarly, non-biologic small molecules such as tofacitinib and baricitinib have not been studied sufficiently with other biologic disease-modifying antirheumatic drugs (DMARDs) to safely recommend their use as dual therapy. Likewise, sufficient data is not currently available to support the safety and efficacy of apremilast use in combination with other agents listed in these criteria.

Rheumatoid Arthritis

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), tocilizumab-aazg (Tyenne), or etanercept (Enbrel)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **rheumatoid arthritis** when the following are met:
      1. Treatment with an oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective or not tolerated, or all are contraindicated (e.g., guidelines direct to methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.)

II. **Abatacept (Orencia), anakinra (Kineret), certolizumab (Cimzia), golimumab (Simponi), sarilumab (Kevzara), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], tocilizumab-aazg (Tyenne), and etanercept (Enbrel) have been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars (adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)) have been ineffective, contraindicated, or not tolerated

III. **Brand Humira** or **Brand Actemra** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
         i. If the request is for brand Humira:
            a. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
         ii. If the request is for brand Actemra:
            a. Treatment with tocilizumab-aazg (Tyenne) has been ineffective, not tolerated, or is contraindicated; **OR**
      2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
      3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **AND**
   D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), and tocilizumab-aazg (Tyenne)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms; **AND**

IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to rheumatoid arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.); **AND**

A. If the request is for **Brand Humira or Brand Actemra**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**

B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. The request is for Brand Humira; **AND**
        a. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
    ii. The request is for Brand Actemra; **AND**
        a. tocilizumab-aazg (Tyenne) has been tried; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **AND**

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the

reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The agents listed above are approved for adult patients with rheumatoid arthritis (RA) based on safety and efficacy data from randomized-controlled trials.

III. The 2021 American College of Rheumatology (ACR) guidelines for rheumatoid arthritis address the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted-synthetic DMARDS (tsDMARDs) such as JAK inhibitors, and biologic DMARDS (bDMARDs) as TNF inhibitors and non-TNF inhibitors. A majority of recommendations are based on low or very low certainty of evidence.

- The 2021 ACR guidelines strongly recommend the use of csDMARD monotherapy (methotrexate preferred) in patients who are DMARD-naïve with moderate-to-severe RA. Recommended csDMARDs include methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. Despite moderate evidence in the SELECT-EARLY study noting higher efficacy of upadacitinib over methotrexate in DMARD-naïve patients with moderate-to-severe RA, there is limited long-term safety data to strongly recommend the use of tsDMARDs (e.g., JAK inhibitors) as first line therapy. Therefore, methotrexate monotherapy remains the preferred first-line therapy over tsDMARDs in DMARD-naïve patients based on established safety and efficacy. Additionally, JAK inhibitors are not FDA approved for use in csDMARD-naïve patients.
- For patients who are DMARD-naïve with low disease activity, initial trial of hydroxychloroquine over other csDMARDs, and sulfasalazine over methotrexate is conditionally recommended.
- For DMARD-naive patients with moderate-to-severe disease activity, methotrexate monotherapy is conditionally recommended over methotrexate in combination with a TNF inhibitor due to low-certainty evidence with combination use. The recommendation is conditional because patients with poor prognostic factors may benefit from a faster onset of action and greater change of improvement with dual therapy.
- In DMARD-naive patients with moderate-to-severe disease activity, methotrexate monotherapy is strongly recommended over the addition of a non-TNF inhibitor or tsDMARD based additional risks of adding a biologic or tsDMARD and low-quality data evaluating superiority over methotrexate monotherapy.
- For patients with moderate-to-severe disease activity despite adequate trial of csDMARD monotherapy, a treat-to-target approach is strongly recommended and the addition of a bDMARD or tsDMARD is conditionally recommended as combination therapy may provide a more rapid treatment response. The recommendation was based on very low certainty of evidence.

- The guidelines conditionally recommend switching to a bDMARD or tsDMARD of a different class over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target, however the recommendation is based on very low-quality evidence supporting greater improvement in disease activity among patients switching therapy classes. There are no current recommendations for using a bDMARD over a tsDMARD, however patients and providers should engage in a shared decision-making approach based on the available safety data of JAK inhibitors.
- The 2021 ACR guidelines have additional recommendations for patient specific populations, including patients with co-morbid heart failure, lymphoproliferative disorder, Hepatitis B infection, nonalcoholic fatty liver disease (NAFLD), persistent hypogammaglobulinemia without infection, and populations with history of serious infection(s).

IV. The 2019 European League Against Rheumatism (EULAR) guidelines follow similar recommendations to the 2021 ACR guidelines, and state that patients who have failed one bDMARD or tsDMARD may switch to an agent from the same class. Studies have demonstrated that primary TNF non-responders have responded to other agents of the same mechanism of action.

V. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

VI. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

VII. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of

death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References:

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Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), tocilizumab-aazg (Tyenne), or etanercept (Enbrel)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **Polyarticular Juvenile Idiopathic Arthritis (PJIA)** when the following is met:
      1. Treatment with at least one oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective, contraindicated, or not tolerated. Guidelines direct to use of methotrexate, sulfasalazine,

hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.

II. **Abatacept (Orencia), sarilumab (Kevzara), certolizumab (Cimzia), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Request is for abatacept (Orencia) or non-preferred adalimumab biosimilars; **OR**
      1. Request is for sarilumab (Kevzara); **AND**
         i. Member weighs 63 kilograms or more; **AND**
   C. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], tocilizumab-aazg (Tyenne), and etanercept (Enbrel) have been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars (adalimumab -bwwd (Hadlima) and adalimumab -adaz (Adalimumab-ADAZ)) have been ineffective, contraindicated, or not tolerated

III. **Brand Humira** or **Brand Actemra** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
         i. If the request is for brand Humira:
            a. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
         ii. If the request is for Brand Actemra:
            a. tocilizumab-aazg (Tyenne) has been tried; **OR**
      2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
      3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:

i. Was life-threatening; **OR**
ii. Required hospitalization; **OR**
iii. Required intervention to prevent impairment or damage; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), and tocilizumab-aazg (Tyenne)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat polyarticular juvenile idiopathic arthritis or another auto-immune condition (e.g., Humira, Xeljanz, Infliximab, etc.); **AND**

A. If the request is for **Brand Humira or Brand Actemra**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; AND

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
   i. The request is for Brand Humira; **AND**
      a. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; OR
   ii. The request is for Brand Actemra; **AND**
      a. tocilizumab-aazg (Tyenne) has been tried; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:

i. Was life-threatening; **OR**
ii. Required hospitalization; **OR**
iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Juvenile idiopathic arthritis (JIA) is a grouping of inflammatory disorders that affect children. Polyarticular juvenile idiopathic arthritis (PJIA) is a subset of JIA, which is defined by the presence arthritis in five or more joints during the first six months of illness. Other subsets of JIA include ERA, oligoarthritis (less than five joints affected), systemic juvenile idiopathic arthritis (SJIA; fever, rash, hepatic/splenic/lymphatic involvement), and psoriatic arthritis (psoriasis and dactylitis). While these are distinct disease states, their pathogenesis and presentation are similar so there is significant overlap in effective treatments.

III. Adalimumab (Humira), etanercept (Enbrel), abatacept (Orencia), and tocilizumab (Actemra) are approved for pediatric patients greater than two years of age with PJIA based on safety and efficacy data from randomized-controlled trials.

IV. The 2019 ACR JIA guidelines strongly recommend initial therapy with a DMARD for all patients with JIA and active polyarthritis; methotrexate has the strongest evidence, but sulfasalazine and leflunomide can also be used. Adjunctive therapy with NSAIDs and oral or intra-articular glucocorticoids is common. Regardless of disease activity, initial therapy with a DMARD is recommended over a biologic, though there may be certain situations where a biologic as initial therapy is preferred (i.e., high risk joints such as cervical spine, wrist, or hip involved). ACR notes that while initial treatment with biologics was studied in the TREAT-JIA and ACUTE-JIA studies, results were not deemed conclusive enough to make recommendations for biologics as initial therapy at this time. For patients with continued moderate to high disease activity, the guidelines recommend adding a TNF inhibitor, abatacept, or tocilizumab as second-line. The ACR guidelines make a conditional recommendation for switching to non-TNF inhibitor biologics (tocilizumab and abatacept) in patients receiving a TNF inhibitor with continued moderate or

high disease activity. It is noted that a second TNF inhibitor may be appropriate for patients who had a good initial response to the first TNF inhibitor but had secondary failure due to suspected drug antibodies developing, and that this conditional recommendation stems from data in adult rheumatoid arthritis patients. Juvenile psoriatic arthritis follows the same treatment paradigm.

V. A phase 3 double-blind, randomized, placebo-controlled withdrawal study (PROPEL) evaluated the efficacy and safety of tofacitinib (Xeljanz) in patients aged 2-17 years old with active PJIA and who had inadequate response to at least one DMARD or biologic DMARD. The primary endpoint evaluated the occurrence of disease flare at week 44 and was found to be statistically significantly lower in tofacitinib (Xeljanz) group vs the placebo group (29.2 % vs 59.2%, p-value=0.0031). The secondary endpoint found improvements from baseline in questionnaires JIA ACR 30/50/70 and Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) in tofacitinib vs placebo. Some limitations to the study include potential bias in the open label arm of the study, and the study is unpublished with limited information such as the population of patents currently on DMARD or oral glucocorticoid.

VI. Sarilumab (Kevzara) is approved for active PJIA in pediatric patients who weigh 63 kg or greater. Use of sarilumab (Kevzara) in this patient population is supported by evidence from adequate and well-controlled studies of sarilumab (Kevzara) in adults with RA, pharmacokinetic data from adult patients with RA, and a pharmacokinetic, pharmacodynamic, dose-finding, and safety study in pediatric patients with PJIA 2 years of age and older. Sarilumab (Kevzara) is not approved in pediatric patients weighing less than 63 kg because of the lack of an appropriate dosage form nor is the safety and efficacy established in those under 2 years of age.

VII. In September 2024, certolizumab (Cimzia) was approved in PJIA for patients aged two and older. This approval was based on the efficacy of adult patients in RA combined with pharmacokinetic studies in pediatrics. Additionally, an open-label study (PASCAL) was assessed in 193 patients aged two to 17 after failure of biologic/non-biologic DMARD. Efficacy was assessed as secondary endpoints at week 24, PASCAL was primarily a PK/safety study; the results were consistent with adult RA study patients. Certolizumab (Cimzia) is given as weight-based dosing for this indication.

VIII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

IX. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a

rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

X. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Enthesitis-Related Arthritis (ERA)

Initial Evaluation

I. **Secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **Enthesitis-Related Arthritis (ERA**) when the following is met:
      1. Treatment with at least one oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective, contraindicated, or not tolerated. Guidelines direct to use of methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat enthesitis-related arthritis (ERA) or another auto-immune condition (e.g., Humira, Xeljanz, Infliximab, etc.).

Supporting Evidence

I. Enthesitis-related arthritis (ERA) is a subset of juvenile idiopathic arthritis (JIA) and is characterized primarily by inflammation of the entheses, or connective tissue between tendon/ligament and bone, and commonly affects sacroiliac or lumbosacral joints. Other subsets of JIA include PJIA, oligoarthritis (less than five joints affected), systemic juvenile idiopathic arthritis (SJIA; fever, rash, hepatic/splenic/lymphatic involvement) and psoriatic arthritis (psoriasis and dactylitis). While these are distinct disease states, their pathogenesis and presentation are similar so there is significant overlap in effective treatments.
II. Secukinumab (Cosentyx) was approved for pediatric patients aged four years or older with ERA based on safety and efficacy from a phase 3 study (JUNIPERA) of children aged 2-17 years with a diagnosis of active ERA or juvenile psoriatic arthritis with an inadequate response or intolerance to at least 1 NSAID and at least 1 DMARD. The majority (67.6% of juvenile psoriatic arthritis, 63.5% of ERA) of patients were taking concomitant methotrexate throughout the study. The primary endpoint was time to flare over a 92-week period, which was met with a statistically significant longer time to flare in the secukinumab group compared to placebo group for both indications; risk of flare was reduced by 53% in ERA (HR 0.47, 95% CI 0.17-1.32) and 85% in juvenile psoriatic arthritis (HR 0.15, 95% CI 0.04-0.56).

Improvements in the secondary endpoint JIA ACR 30/50/70/90 were also seen in the intervention group relative to placebo. No new safety signals were discovered, and adverse effects were consistent with the established safety profile of secukinumab.

III. The 2019 ACR JIA guidelines provide recommendations for enthesitis, which include ERA, psoriatic arthritis, and undifferentiated arthritis, all of which fall under the JIA umbrella. For patients with ERA, initial therapy with an NSAID is recommended. In the second-line setting, ACR provides a conditional recommendation for TNF inhibitors over DMARD, though this is based on low-quality evidence; this recommendation is rooted in retrospective cohort and phase 3 studies of etanercept and adalimumab for several different subtypes of JIA, including ERA, which provided mixed signals that biologics are more effective than placebo or no comparator, but the majority of included patients had previously been treated with at least one NSAID and DMARD. It has also been suggested that methotrexate is not as effective at managing axial manifestations of ERA. However, DMARDs remain a viable first-line option for ERA patients given their well-established efficacy and safety profile, especially in those with mild disease or concomitant active polyarthritis. Age-appropriate biologics approved for ERA, PJIA or juvenile psoriatic arthritis should be reserved for subsequent therapy.

IV. While other biologics have been evaluated for use in ERA or other JIA subtypes, only secukinumab (Cosentyx) is FDA-approved for ERA. Notably, etanercept and adalimumab have undergone one phase 3 study each in ERA patients but neither have pursued FDA approval. In a 12-week randomized, double-blind study of ERA patients aged 6-18 years (n=46) followed by a 180-week open label single-arm extension, adalimumab was found to provide a statistically significant greater reduction in the number of active joints with arthritis at week 12 compared to placebo, but the majority of secondary endpoints, including ACR 30/50/70/90, were not met. In a 12-week single-arm open-label study of JIA patients, including ERA, extended oligoarticular JIA and PsA patients aged 12-17 years (n=127) with an 86-week single-arm extension, a greater proportion of patients treated with etanercept achieved JIA ACR30 compared to historical placebo data. No new safety concerns arose during studies. At this time, quality of these data is considered low due to small sample size, single-arm open-label study design, and lack of clinically meaningful endpoints being met.

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Systemic Juvenile Idiopathic Arthritis (SJIA)

Initial Evaluation

I. **Tocilizumab-aazg (Tyenne)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **active SJIA** when the following are met:
      1. Treatment with at least one NSAID (e.g., ibuprofen, naproxen, indomethacin, meloxicam, celecoxib, etc.) or glucocorticoid (i.e., prednisone, hydrocortisone, methylprednisolone, etc.) has been ineffective, contraindicated, or not tolerated; **OR**
      2. Patient has severe active disease as indicated by one of the following:
         i. Suspected early macrophage activating syndrome (MAS)
         ii. Disabling polyarthritis
         iii. Serositis

II. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with tocilizumab-aazg (Tyenne) has been ineffective, contraindicated, or not tolerated.

III. **Abatacept (Orencia)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with anakinra (Kineret) AND tocilizumab-aazg (Tyenne) has been ineffective, contraindicated, or not tolerated.

IV. **Brand Actemra** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. Treatment with tocilizumab-aazg (Tyenne) have been ineffective, not tolerated, or are contraindicated; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: anakinra (Kineret) and abatacept (Orencia).

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat juvenile idiopathic arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Infliximab, etc.); **AND**
    a. If the request is for **brand Actemra**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    b. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
        i. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**

1. Tocilizumab-aazg (Tyenne) has been tried; **OR**

ii. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**

iii. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:

1. Was life-threatening; **OR**
2. Required hospitalization; **OR**
3. Required intervention to prevent impairment or damage

Supporting Evidence

I. Anakinra (Kineret) does not have FDA approval for SJIA but did gain approval recently by the European Medicines Agency for this indication in 2018. A prospective trial examined 42 children with new-onset disease after no response to a seven-day trial of NSAIDs. Rapid improvement was seen, with inactive disease noted in 55% and 71% of patients at one and three months, respectively. A similar rate of response was seen in a small RCT (ANAJIS) to that seen in the tocilizumab trial and is described below in terms of ACR30.

II. Tocilizumab is approved for treatment of active SJIA in patients two years and older. In a RCT of 112 children with SJIA for greater than six months, who had an inadequate response to NSAIDs and glucocorticoids, tocilizumab patients were more likely to achieve JIA ACR30 response by week 12 compared to placebo (85% vs 24%, $p<0.001$).

III. The SJIA guidelines updated in 2013 by the ACR note that NSAIDs are recommended as an initial treatment approach. However, based off expert opinion, monotherapy is inappropriate for patients with an MD global assessment score of 5 or greater (0-10 scale), indicating severe disease. Likewise, it is noted that macrophage activation syndrome (MAS) which occurs in approximately 10% of SJIA patients, is a severe, life-threatening condition and delay in IL-1 or IL-6 inhibitor therapy should not occur in this scenario. Anakinra (Kineret) is recommended as an initial treatment option in patients with severely active disease, as well as for patients with continued disease activity after treatment with glucocorticoid or NSAID monotherapy. For those patients who have tried both anakinra (Kineret) and tocilizumab (Actemra) sequentially, abatacept (Orencia) is recommended based off expert opinion. A subset of 37 children with systemic JIA was examined in comparison to placebo in a RCT. After four months of treatment in the initial lead-in period, 24 of 37 patients (65%) treated with abatacept had a ACR30 response, which was similar to response rates seen in patients included with other JIA subtypes.

IV. TNF inhibitors demonstrate greater efficacy in patients with nonsystemic JIA compared to SJIA. For instance, a study of 45 children who had systemic symptoms at the start of TNF inhibitor

therapy noted lower rates of remission and a high frequency of disease flare (24% and 45%, respectively).

V. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

VI. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

VII. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Psoriatic Arthritis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma), etanercept (Enbrel), or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist or dermatologist; **AND**
   B. A diagnosis of active **psoriatic arthritis** when the following are met:
      1. Treatment with non-biologic, non-specialty oral small molecules (OSMs) such as methotrexate, leflunomide, sulfasalazine, or cyclosporine has been ineffective, contraindicated, or not tolerated; **OR**
      2. Presence of active, severe disease as indicated by provider assessment and the presence of at least one of the following:
         i. Erosive disease
         ii. Elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)
         iii. Long-term damage interfering with function (e.g., joint deformities, vision loss)

iv. Major impairment of quality of life due to high disease activity at many sites (including dactylitis, enthesitis,) or functionally limiting arthritis at a few sites

II. **Abatacept (Orencia), certolizumab (Cimzia), golimumab (Simponi), ixekizumab (Taltz), apremilast (Otezla), guselkumab (Tremfya), risankizumab (Skyrizi), bimekizumab (Bimzelx), non-preferred ustekinumab biosimilars, or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:

A. Criteria I(A)-I(B) above are met; **AND**
B. Member is 18 years of age or older; **AND**
   1. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], etanercept (Enbrel), and secukinumab (Cosentyx) have been ineffective, contraindicated, or not tolerated; **AND**
      i. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars (adalimumab -bwwd (Hadlima) and adalimumab -adaz (Adalimumab-ADAZ)) have been ineffective, contraindicated, or not tolerated; **OR**
      ii. If the request is for non-preferred ustekinumab biosimilars, at least three preferred ustekinumab biosimilars (ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)) have been ineffective, contraindicated, or not tolerated; **OR**
C. Member is two to five years of age; **AND**
   1. Treatment with secukinumab (Cosentyx) has been ineffective, contraindicated, or not tolerated; **OR**
D. Member is six to 17 years of age; **AND**
   1. Treatment with secukinumab (Cosentyx) and ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], have been ineffective, contraindicated, or not tolerated.

III. **Brand Humira or brand Stelara** may be considered medically necessary when the following criteria below are met:

A. Criteria I(A)-I(CB) above are met; **AND**
B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. If the request is for brand Humira, treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
    ii. If the request is for brand Stelara, treatment with ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), AND ustekinumab-stba (Steqeyma) have been ineffective, not tolerated, or are contraindicated; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], etanercept (Enbrel) and secukinumab (Cosentyx).

**Clinical note: If a patient has a diagnosis of both plaque psoriasis and psoriatic arthritis, approval of the requested medication can be made as long as the patient fulfills the criteria for at least one of the disease states and associated medication criteria.*

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat psoriatic arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.); **AND**

A. If the request is for **Brand Humira or Brand Stelara**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
    i. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        a. If the request is for brand Humira, at least two adalimumab biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
        b. If the request is for brand Stelara, at least three ustekinumab biosimilars have been tried [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)]; **OR**
    ii. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    iii. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        a. Was life-threatening; **OR**
        b. Required hospitalization; **OR**
        c. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering

competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are approved for adult patients in the treatment of psoriatic arthritis based on safety and efficacy data from randomized-controlled trials. Additionally, secukinumab (Cosentyx) was approved for pediatric patients aged two years or older with psoriatic arthritis based on safety and efficacy from a phase 3 study (JUNIPERA) of children aged 2-17 years with a diagnosis of active enthesitis-related arthritis or juvenile psoriatic arthritis with an inadequate response or intolerance to at least 1 NSAID and at least 1 DMARD. See PJIA section for additional study details.

III. The 2018 ACR guidelines for psoriatic arthritis make a conditional recommendation for starting a TNF inhibitor over an OSM as a first-line option for patients who are treatment-naïve with active psoriatic arthritis. This recommendation is based on low- to very-low quality of evidence. Many of the studies in which greater benefit was seen in terms of disease severity or radiographic progression compared methotrexate to TNF inhibitors, however, most patients included in these groups were not truly treatment naïve to OSM medications. Guidelines note that OSM can be used first-line in naïve patients who do not have severe PsA, severe PsO, prefers oral therapy, or has contraindications to TNF inhibitors. In patients who continue to have active disease despite OSM treatment, it is recommended to switch to a TNF inhibitor rather than trying a different OSM.

IV. According to the 2019 ACR guidelines for juvenile idiopathic arthritis (JIA), which have been described in the PJIA section, treatment of pediatric PsA is similar to adult PsA: oral DMARD as first line, TNF inhibitors or other biologics as second line. Regardless of the level of disease activity, initial therapy with a DMARD is recommended over a biologic. However, initial therapy with a biologic may be preferred for patients with risk factors for/involvement of high-risk joints (cervical spine, wrist, hip), high disease activity, and/or those judged by their physician to be at risk of disabling joint disease.

V. A systematic review of RCTs published in 2015 examined differences in terms of ACR20 response with biologic versus synthetic DMARDs. A statistically significant benefit was not demonstrated with methotrexate, cyclosporine, or sulfasalazine. Leflunomide did demonstrate a statistically significant benefit, though the magnitude of benefit was lower than all of the biologic DMARDs analyzed. There are many limitations to this review, such as a large proportion of trials/data that only included a small number of patients (less than 100). A recent study compared the TNF inhibitor etanercept to methotrexate monotherapy in patients naïve to both biologics and methotrexate. Patients treated with etanercept were statistically more likely to achieve ACR20 response at week 24 compared to the methotrexate monotherapy group (difference 9.2%, 95% CI 1.0 to 17.3, p = 0.029).

VI. The 2018 ACR guidelines for psoriatic arthritis also conditionally recommend for use of a TNF inhibitor biologics over IL-17 inhibitors (ixekizumab, secukinumab) or IL-12/23 inhibitors (ustekinumab). In January 2022, the latest agent, risankizumab, an IL-23 inhibitor, was

approved; however, the guidelines have not been updated with regard to place in therapy for risankizumab or other IL-23 inhibitors, such as guselkumab.

VII. The 2021 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) clinical guidelines is the latest international clinical guidance document which makes evidence-based treatment recommendations for adults with PsA, utilizing a domain-based approach, spanning six domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis and nail psoriasis.

- In patients presenting with peripheral arthritis and treatment naïve to conventional synthetic disease modifying antirheumatic drugs (csDMARDs) (methotrexate, sulfasalazine, or leflunomide), csDMARDs are strongly recommended as a first-line treatment option.
- For patients with inadequate response to csDMARDs, TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors, IL-12/23 inhibitors, JAK inhibitors, and PDE4 inhibitors are strongly recommended on the basis of high-moderate quality evidence. Based on current evidence, including head-to-head studies TNF inhibitors, IL-17 inhibitors, and JAK inhibitors are equally recommended. There are no studies comparing IL-23 inhibitors with other bDMARDs or JAK inhibitors.
- For patients with enthesitis, dactylitis, and nail psoriasis TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, IL-23 inhibitors, JAK inhibitors, and PDE4 inhibitors are equally strongly recommended, while methotrexate carries a conditional recommendation for these disease manifestations. For plaque psoriasis, topical therapies, methotrexate, famarate, and bDMARDs all carry a strong recommendation.

VIII. Expanded approval of ustekinumab for active psoriatic arthritis for children and adolescents was based on data extrapolation from multiple phase 3 studies for adults and pediatric patients with moderate to severe plaque psoriasis (PSTELLAR, CADMUS, and CADMUS Jr) and multiple phase 3 studies for adults with active psoriatic arthritis (PSUMMIT I and II). Pharmacokinetic and safety data analysis in pediatric patients with active psoriasis and psoriatic arthritis are comparable to adult data in regard to pharmacokinetic concentrations and disease-medication response, with no additional safety issues present in the pediatric population (similar with no new safety signals when compared pediatric AE to adult AE rates).

IX. Expanded approval of abatacept (Orencia) and etanercept (Enbrel) in pediatric patients ages two and up for psoriatic arthritis was based on data extrapolation from studies in adult populations (PsA and RA) and pediatric patients with PJIA (and PsO for Enbrel). Observed trough concentrations were found to be generally comparable between adults and pediatric patients. Pharmacokinetic exposure is expected to be comparable between adult and pediatric patients with PsA.

X. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XI. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XII. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Ankylosing Spondylitis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel), or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **Ankylosing Spondylitis (Axial Spondyloarthritis)** when the following are met:
      1. High disease activity (e.g., bothersome chronic neck, back, or hip pain, peripheral joint pain, morning stiffness, fatigue, objective signs of inflammation, functional

impairment, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4, Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥2.1); **AND**

2. Treatment with at least two different Nonsteroidal Anti-Inflammatory Drugs NSAIDs (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated**.**

II. **Certolizumab (Cimzia), ixekizumab (Taltz), golimumab (Simponi), bimekizumab (Bimzelx), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:

A. Criteria I(A)-I(B) above are met; **AND**

B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), AND secukinumab (Cosentyx) have been ineffective, contraindicated, or not tolerated; **AND**

1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars (adalimumab -bwwd (Hadlima) and adalimumab -adaz (Adalimumab-ADAZ)) have been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:

A. Criteria I(A)-I(B) above are met; **AND**

B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**

C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. Treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**

iii. Required intervention to prevent impairment or damage; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: etanercept (Enbrel) and secukinumab (Cosentyx)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms; **AND**

IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat ankylosing spondylitis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Infliximab, etc.); **AND**

A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**

B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
   i. Treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
2. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
   i. Was life-threatening; **OR**
   ii. Required hospitalization; **OR**
   iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are approved for adult patients in the treatment of ankylosing spondylitis based on safety and efficacy data from randomized-controlled trials.

III. Axial spondyloarthritis (SpA or axSpA) is an umbrella term which is comprised of ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Ankylosing spondylitis (AS) is an older term and is used interchangeably with the term axial spondyloarthritis (SpA or axSpA). AS or axSpA or SpA or r-axSpA and nr-axSpA represent two stages of the same disease: the nr-axSpA represents an earlier stage without definite radiographic sacroiliitis. In contrast, definitive radiographic changes on X-ray are present with AS. However, not all nr-axSpA patients progress to AS. Additionally, it has been shown that axSpA and nr-axSpA are largely similar with regard to burden of disease, including the presence of comorbidities, treatment received and response. Since typical signs and symptoms of SpA do not depend on the degree of SI joint damage, patients' symptoms present similarly. On average, loss of function and work impairment in nr-axSpA and AS are comparable. Both manifestations deserve the same level of treatment and care. Clinical guideline recommendations for both axSpA and nr-axSpA follow the same recommendations with variable quality of evidence.

IV. SpA is a relapsing remitting disease. When the disease is active it is characterized by chronic low back pain, swelling, and inflammation with a usual onset before 45 years of age. The disease is also commonly associated with insidious onset, fatigue, morning stiffness, improvement of symptoms with exercise, HLA-B27 positivity, elevated markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Peripheral manifestations are also possible and include peripheral arthritis, enthesitis, and dactylitis. Peripheral arthritis commonly presents as arthritis of the knees, ankles etc., enthesitis which is inflammation of entheses, (site of insertion of ligaments, tendons, joint capsule, or fascia to bone) commonly manifests as swelling at the heels, at the insertion of the Achilles tendon, or at the insertion of the plantar fascia ligament into the calcaneus, and dactylitis (sausage digits) manifests as swollen digits. Lastly, extramusculoskeletal manifestations (EMMs) are possible, which include

uveitis/iritis, skin psoriasis, and inflammatory bowel disease (IBD). In patients SpA and comorbid EMMs, comorbidities often guide therapeutic choices.

V. Diagnosis of SpA is challenging which requires weighing of multiple risk factors and is based on clinical presentation in combination with laboratory and imaging tests and exclusion of other more likely diagnoses. Importantly, diagnosis is not made based on Assessment of SpondyloArthritis international society (ASAS) axSpA classification criteria, which is only used for research purposes. Although inflammatory back pain alone is not sufficient to diagnose SpA, its presence is an important initial step in preselection of patients with a high probability of SpA. Other typical features of SpA include good initial response to NSAIDs, peripheral manifestations, EMMs, positive family history, elevated lab markers such CRP and ESR, and HLA-B27 positivity. Imaging (plain radiography or X-ray) can detect sacroiliitis of the axial skeleton in patients with radiographic changes (AS). Patients that are not positive for sacroiliitis by plain imaging or X-rays can undergo MRI to detect inflammatory changes of the joints. Patients without abnormalities on imaging (X-ray or MRI) but with other SpA typical features (symptoms, lab markers, etc.) can be diagnosed with nr-axSpA.

VI. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) are scoring instruments that assess disease activity when monitoring patients with SpA. ASDAS incorporates patient perspectives of their disease activity and includes CRP as an objective measure of inflammation while BASDAI reflects only the patient perspective. Both instruments incorporate questions that assess the level of fatigue, pain, swelling, discomfort, and morning stiffness. While the 2022 ASAS-EULAR clinical guidelines endorse the use of these instruments in clinical practice to determine when escalation in therapy may be needed and to determine response to treatment, the use of these instruments to determine treatment intensification or baseline disease activity is not strongly recommended in the 2019 ACR/SAA/SPARTAN guidelines. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend regular-interval use and monitoring of a validated AS disease activity measure and conditionally recommend regular-interval use and monitoring of the CRP concentrations or ESR over usual care. The 2019 ACR/SAA/SPARTAN guidelines further note that no studies addressed the effect of routine monitoring of a disease activity measure, such as the BASDAI or the ASDAS, or acute-phase reactants on outcomes in patients with AS. In clinical settings, the use of BASDAI and ASDAS instruments is not uniformly adopted and other factors other than disease activity often play a role when making treatment decisions. Medical necessity for treatment escalation to a biologic or Janus Kinase (JAK) inhibitor requires that patients have high disease activity which may be defined by BASDAI or ASDAS scores if available or could be determined by a positive rheumatologists' opinion to escalate treatment based on prior failure of conventional therapies (e.g., NSAIDs) and a clinical exam which evaluates presence of ongoing bothersome symptoms, as well as laboratory exams that support ongoing inflammation.

VII. The 2019 ACR/SAA/SPARTAN and the 2022 ASAS-EULAR guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% patients responding). No particular NSAID has been determined to be superior in efficacy or safety and guidelines don't recommend a preferred choice. Guidelines recommend that lack of response (or intolerance) to at least two different NSAIDs at maximal doses over one month, or

incomplete responses to at least two different NSAIDs over 2 months, would be adequate trials with which to judge NSAID responsiveness prior to escalating to treatment with Tumor Necrosis Factor (TNF) inhibitors.

VIII. For those patients with inadequate response despite continuous NSAID treatment, the 2019 ACR/SAA/SPARTAN panel recommends the use of TNF inhibitors as the preferred next choice due to experience and familiarity with their long-term safety and toxicity. Guidelines do not recommend any particular TNF inhibitor as the preferred choice. For those patients with continued active disease, the panel conditionally recommends a trial of a different TNF inhibitor over treatment with a non-TNF inhibitor in patients with secondary nonresponse to TNF inhibitor (those that initially responded and subsequently lost response over time). In patients that never responded to a first trial of a TNF inhibitor (primary nonresponse), trial of a different TNF inhibitor is not recommended and use of subsequent biologics of JAK inhibitors is preferred. Patients presenting with peripheral arthritis symptoms have additional treatment options before escalating to a biologic, which include sulfasalazine and local glucocorticoid (GC) injections. GC injections may also be used in patients with isolated sacroiliitis.

IX. In patients with intolerance, contraindications, or loss of efficacy with TNF inhibitors, the 2019 ACR/SAA/SPARTAN guidelines recommend IL-17A inhibitors next, followed by JAK inhibitors. Precautions for cardiovascular risk, malignancy, and thromboembolic events should be considered in patients starting JAK inhibitors. It is unclear whether the increased risk of cardiovascular events and malignancies is specific to a diagnosis of Rheumatoid Arthritis (RA), reflective of a JAK inhibitor class effect, or specific to tofacitinib (Xeljanz). Until more data becomes available, the 2022 ASAS-EULAR guidelines advise against starting JAK inhibitors in specific populations: patients above 50 years of age with one or more cardiovascular risk factor and patients older than 65 years of age.

X. According to the 2022 ASAS-EULAR and 2019 ACR/SAA/SPARTAN guidelines, treatment decisions may differ for patients presenting with EMMs. For example, for those with SpA and comorbid uveitis/iritis, adalimumab, infliximab, golimumab, and certolizumab pegol may be preferred over etanercept as this TNF inhibitor showed contradictory results. Secukinumab was shown to be unsuccessful in patients with non-infectious uveitis while rates of uveitis flares with ixekizumab have not been well-defined. For patients with comorbid inflammatory bowel disease (IBD), TNF inhibitors are preferred (except etanercept which is not effective in IBD). Secukinumab has been associated with the new onset, or exacerbation, of Crohn's disease. Increased risks of IBD exacerbation appear to also occur with ixekizumab. For psoriasis and SpA, guidelines suggest that IL-17 inhibitors may be preferred, however, no comparative data is available on psoriasis patients with axSpA. For the treatment of psoriasis and SpA, a product that is FDA approved for both indications is preferred.

XI. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend against the addition of sulfasalazine or methotrexate to biologic drugs and do not recommend these treatments for those with predominantly axial disease symptoms. This is based off controlled trials demonstrating minimal to no benefit with agents such as sulfasalazine, methotrexate, and leflunomide. Some benefit has been seen in patients with peripheral arthritis, and thus these agents may be considered for patients with ankylosing spondylitis with predominantly

peripheral arthritis symptoms. Similar recommendations are made by the 2022 ASAS/EULAR guidelines.

XII. There is no specific treatment algorithm after primary non-response to biologic (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor therapy. In absence of data showing superiority in the treatment sequence, switching to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or a JAK inhibitor may be considered.

XIII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XIV. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XV. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Non-radiographic Axial Spondyloarthritis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel), or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **Non-radiographic Axial Spondyloarthritis** when the following are met:
      1. High disease activity (e.g., bothersome chronic neck, back, or hip pain, peripheral joint pain, morning stiffness, fatigue, objective signs or inflammation, functional impairment, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4, Ankylosing Spondylitis Disease Activity Score (ASDAS) score ≥2.1; **AND**
      2. Treatment with at least two different Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated.

II. **Certolizumab (Cimzia), ixekizumab (Taltz), bimekizumab (Bimzelx), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), AND secukinumab (Cosentyx) has been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars (adalimumab -bwwd (Hadlima) and adalimumab -adaz (Adalimumab-ADAZ)) have been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
         i. Treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
      2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
      2. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **AND**
   D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: etanercept (Enbrel) and secukinumab (Cosentyx)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat non-radiographic axial spondyloarthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Infliximab, etc.); **AND**
    A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
            i. Treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
        2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
        3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
            i. Was life-threatening; **OR**
            ii. Required hospitalization; **OR**
            iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in

promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Currently, certolizumab pegol, ixekizumab, secukinumab, upadacitinib, and bimekizumab are the only FDA approved agent for adults with non-radiographic axial spondyloarthritis. All FDA approved drugs were studied in Phase 3 studies which demonstrated statistically significant improvements in ASAS 40 response and other outcomes. Other TNF inhibitors are approved in Europe for this indication, have demonstrated efficacy in RCTs, and are utilized frequently in clinical practice. For instance, a study of 192 patients taking adalimumab demonstrated significant improvement compared to placebo in ASAS40 response by week 12 in patients with non-radiographic disease (36% vs 15%, $p < 0.001$). Likewise, etanercept and golimumab have also been approved by the European Medicines Agency, and the 2022 ASAS/EULAR guidelines note that efficacy in regard to musculoskeletal signs and symptoms appears comparable based off indirect comparison.

III. Axial spondyloarthritis (SpA or axSpA) is an umbrella term which is comprised of ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Ankylosing spondylitis (AS) is an older term and is used interchangeably with the term axial spondyloarthritis (SpA or axSpA). AS or axSpA or SpA or r-axSpA and nr-axSpA represent two stages of the same disease: the nr-axSpA represents an earlier stage without definite radiographic sacroiliitis. In contrast, definitive radiographic changes on X-ray are present with AS. However, not all nr-axSpA patients progress to AS. Additionally, it has been shown that axSpA and nr-axSpA are largely similar with regard to burden of disease, including the presence of comorbidities, treatment received and response. Since typical signs and symptoms of SpA do not depend on the degree of SI joint damage, patients' symptoms present similarly. On average, loss of function and work impairment in nr-axSpA and AS are comparable. Both manifestations deserve the same level of treatment and care. Clinical guideline recommendations for both axSpA and nr-axSpA follow the same recommendations with variable quality of evidence.

IV. SpA is a relapsing remitting disease. When the disease is active it is characterized by chronic low back pain, swelling, and inflammation with a usual onset before 45 years of age. The disease is also commonly associated with insidious onset, fatigue, morning stiffness, improvement of symptoms with exercise, HLA-B27 positivity, elevated markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Peripheral manifestations are also possible and include peripheral arthritis, enthesitis, and dactylitis. Peripheral arthritis commonly presents as arthritis of the knees, ankles etc., enthesitis which is inflammation of

entheses, (site of insertion of ligaments, tendons, joint capsule, or fascia to bone) commonly manifests as swelling at the heels, at the insertion of the Achilles tendon, or at the insertion of the plantar fascia ligament into the calcaneus, and dactylitis (sausage digits) manifests as swollen digits. Lastly, extramusculoskeletal manifestations (EMMs) are possible, which include uveitis/iritis, skin psoriasis, and inflammatory bowel disease (IBD). In patients SpA and comorbid EMMs, comorbidities often guide therapeutic choices.

V. Per 2019 ACR/SAA/SPARTAN non-radiographic axial spondyloarthritis treatment guidelines, the panel strongly recommends treatment with TNF inhibitors over no treatment with TNF inhibitors. Moreover, the panel conditionally recommends treatment with TNF inhibitors over treatment with secukinumab or ixekizumab and conditionally recommends treatment with secukinumab or ixekizumab over tofacitinib. In patients with primary nonresponse to the first TNF inhibitor, the panel conditionally recommends switching to secukinumab or ixekizumab over switching to a different TNF inhibitor. A systematic review by Corbett et al published in 2016 demonstrated significant improvement in disease state measures such as the ASAS20 and BASDAI50 in patients with non-radiographic axial spondyloarthritis taking TNF inhibitors such as adalimumab, certolizumab pegol, etanercept, and infliximab.

VI. Diagnosis of SpA is challenging which requires weighing of multiple risk factors and is based on clinical presentation in combination with laboratory and imaging tests and exclusion of other more likely diagnoses. Importantly, diagnosis is not made based on Assessment of SpondyloArthritis international society (ASAS) axSpA classification criteria, which is only used for research purposes. Although inflammatory back pain alone is not sufficient to diagnose SpA, its presence is an important initial step in preselection of patients with a high probability of SpA. Other typical features of SpA include good initial response to NSAIDs, peripheral manifestations, EMMs, positive family history, elevated lab markers such CRP and ESR, and HLA-B27 positivity. Imaging (plain radiography or X-ray) can detect sacroiliitis of the axial skeleton in patients with radiographic changes (AS). Patients that are not positive for sacroiliitis by plain imaging or X-rays can undergo MRI to detect inflammatory changes of the joints. Patients without abnormalities on imaging (X-ray or MRI) but with other SpA typical features (symptoms, lab markers, etc.) can be diagnosed with nr-axSpA.

VII. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) are scoring instruments that assess disease activity when monitoring patients with SpA. ASDAS incorporates patient perspectives of their disease activity and includes CRP as an objective measure of inflammation while BASDAI reflects only the patient perspective. Both instruments incorporate questions that assess the level of fatigue, pain, swelling, discomfort, and morning stiffness. While the 2022 ASAS-EULAR clinical guidelines endorse the use of these instruments in clinical practice to determine when escalation in therapy may be needed and to determine response to treatment, the use of these instruments to determine treatment intensification or baseline disease activity is not strongly recommended in the 2019 ACR/SAA/SPARTAN guidelines. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend regular-interval use and monitoring of a validated AS disease activity measure and conditionally recommend regular-interval use and monitoring of the CRP concentrations or ESR over usual care. The 2019 ACR/SAA/SPARTAN guidelines further note that no studies addressed

the effect of routine monitoring of a disease activity measure, such as the BASDAI or the ASDAS, or acute-phase reactants on outcomes in patients with AS. In clinical settings, the use of BASDAI and ASDAS instruments is not uniformly adopted and other factors other than disease activity often play a role when making treatment decisions. Medical necessity for treatment escalation to a biologic or Janus Kinase (JAK) inhibitor requires that patients have high disease activity which may be defined by BASDAI or ASDAS scores if available or could be determined by a positive rheumatologists' opinion to escalate treatment based on prior failure of conventional therapies (e.g., NSAIDs) and a clinical exam which evaluates presence of ongoing bothersome symptoms, as well as laboratory exams that support ongoing inflammation.

VIII. The 2019 ACR/SAA/SPARTAN and the 2022 ASAS-EULAR guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% patients responding). No particular NSAID has been determined to be superior in efficacy or safety and guidelines don't recommend a preferred choice. Guidelines recommend that lack of response (or intolerance) to at least two different NSAIDs at maximal doses over one month, or incomplete responses to at least two different NSAIDs over 2 months, would be adequate trials with which to judge NSAID responsiveness prior to escalating to treatment with Tumor Necrosis Factor (TNF) inhibitors.

IX. For those patients with inadequate response despite continuous NSAID treatment, the 2019 ACR/SAA/SPARTAN panel recommends the use of TNF inhibitors as the preferred next choice due to experience and familiarity with their long-term safety and toxicity. Guidelines do not recommend any particular TNF inhibitor as the preferred choice. For those patients with continued active disease, the panel conditionally recommends a trial of a different TNF inhibitor over treatment with a non-TNF inhibitor in patients with secondary nonresponse to TNF inhibitor (those that initially responded and subsequently lost response over time). In patients that never responded to a first trial of a TNF inhibitor (primary nonresponse), trial of a different TNF inhibitor is <u>not</u> recommended and use of subsequent biologics of JAK inhibitors is preferred. Patients presenting with peripheral arthritis symptoms have additional treatment options before escalating to a biologic, which include sulfasalazine and local glucocorticoid (GC) injections.

X. In patients with intolerance, contraindications, or loss of efficacy with TNF inhibitors, the 2019 ACR/SAA/SPARTAN guidelines recommend IL-17A inhibitors next, followed by JAK inhibitors. Precautions for cardiovascular risk, malignancy, and thromboembolic events should be considered in patients starting JAK inhibitors. It is unclear whether the increased risk of cardiovascular events and malignancies is specific to a diagnosis of Rheumatoid Arthritis (RA), reflective of a JAK inhibitor class effect, or specific to tofacitinib (Xeljanz). Until more data becomes available, the 2022 ASAS-EULAR guidelines advise against starting JAK inhibitors in specific populations: patients above 50 years of age with one or more cardiovascular risk factor and patients older than 65 years of age.

XI. According to the 2022 ASAS-EULAR and 2019 ACR/SAA/SPARTAN guidelines, treatment decisions may differ for patients presenting with EMMs. For example, for those with SpA and comorbid uveitis/iritis, adalimumab, infliximab, golimumab, and certolizumab pegol may be preferred over etanercept as this TNF inhibitor showed contradictory results. Secukinumab was

shown to be unsuccessful in patients with non-infectious uveitis while rates of uveitis flares with ixekizumab have not been well-defined. For patients with comorbid inflammatory bowel disease (IBD), TNF inhibitors are preferred (except etanercept which is not effective in IBD). Secukinumab has been associated with the new onset, or exacerbation, of Crohn's disease. Increased risks of IBD exacerbation appear to also occur with ixekizumab. For psoriasis and SpA, guidelines suggest that IL-17 inhibitors may be preferred, however, no comparative data is available on psoriasis patients with axSpA. For the treatment of psoriasis and SpA, a product that is FDA approved for both indications is preferred.

XII. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend against the addition of sulfasalazine or methotrexate to biologic drugs and do not recommend these treatments for those with predominantly axial disease symptoms. This is based off controlled trials demonstrating minimal to no benefit with agents such as sulfasalazine, methotrexate, and leflunomide. Some benefit has been seen in patients with peripheral arthritis, and thus these agents may be considered for patients with ankylosing spondylitis with predominantly peripheral arthritis symptoms. Similar recommendations are made by the 2022 ASAS/EULAR guidelines.

XIII. There is no specific treatment algorithm after primary non-response to biologic (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor therapy. In absence of data showing superiority in the treatment sequence, switching to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or a JAK inhibitor may be considered.

XIV. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XV. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XVI. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar.

Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Plaque Psoriasis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma), etanercept (Enbrel), or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by or in consultation with a dermatologist; **AND**
   B. A diagnosis of **moderate to severe plaque psoriasis** when the following are met:
      1. Chronic disease (greater than 6 months), and at least 10% of body surface area is involved or involves areas of the face, ears, hands, feet or genitalia; **AND**
      2. Treatment with the following has been ineffective or not tolerated, or all are contraindicated:
         i. Phototherapy (UVB or PUVA); **OR**
         ii. At least one non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.)

II. **Brodalumab (Siliq), certolizumab (Cimzia), guselkumab (Tremfya), ixekizumab (Taltz), risankizumab (Skyrizi), bimekizumab (Bimzelx), non-preferred ustekinumab biosimilars, or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], etanercept (Enbrel), and secukinumab (Cosentyx) have been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab -bwwd (Hadlima) and adalimumab -adaz (Adalimumab-ADAZ)] have been ineffective, contraindicated, or not tolerated; **OR**
      2. If the request is for non-preferred ustekinumab biosimilars, at least three preferred ustekinumab biosimilars [ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)] have been ineffective, contraindicated, or not tolerated.

III. **Apremilast (Otezla)** may be considered medically necessary when the following criteria are met:
   A. A diagnosis of one of the following:
      1. **Mild to moderate plaque psoriasis** and the following are met:

i. Member has chronic disease (greater than 6 months), and a body surface area under 10% unless areas of the face, ears, hands, feet, genitalia are involved (moves to moderate-severe disease); **AND**
ii. Treatment with the following has been ineffective or not tolerated, or all are contraindicated:
    a. Phototherapy (UVB or PUVA) unless it is contraindicated: **AND**
    b. Treatment with at least <u>two</u> of the following groups has been ineffective or not tolerated, unless ALL are contraindicated:
        i. Group 1: Topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
        ii. Group 2: Topical calcineurin inhibitors (e.g., pimecrolimus cream, tacrolimus ointment)
        iii. Group 3: Topical vitamin D analogue (e.g., calcipotriene)
        iv. Group 4: Topical retinoid (i.e., tazarotene); **OR**

2. **Moderate to severe plaque psoriasis** and the following are met:
    i. Member is being managed by, or in consultation with, a dermatologist; **AND**
    ii. Chronic disease (greater than 6 months), and at least 10% of body surface area is involved or involves areas of the face, ears, hands, feet or genitalia; **AND**
    iii. Treatment with the following has been ineffective or not tolerated, or all are contraindicated:
        a. Phototherapy (UVB or PUVA); **OR**
        b. At least one non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.); **AND**
    iv. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], etanercept (Enbrel), and secukinumab (Cosentyx) have been ineffective, contraindicated, or not tolerated.

IV. **Brand Humira or Brand Stelara** may be considered medically necessary when the following criteria below are met:
    A. Criteria I(A)-I(B) above are met; **AND**
    B. In the absence of a drug shortage, coverage of the multi-source brand drug is to be considered medically necessary when the prescriber is requesting the multi-source brand drug due to a documented adverse reaction to a biosimilar product; **AND**
    C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. If the request is for **brand Humira,** treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
    ii. If the request is for **brand Stelara**, treatment with ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), AND ustekinumab-stba (Steqeyma) have been ineffective, not tolerated, or are contraindicated; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **AND**

B. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-adaz (Adalimumab-ADAZ), adalimumab-bwwd (Hadlima)], ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], etanercept (Enbrel) and secukinumab (Cosentyx).

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat plaque psoriasis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Rinvoq, etc.); **AND**
    A. If the request is for **Brand Humira or Brand Stelara**: In the absence of a drug shortage, coverage of the multi-source brand drug is to be considered medically necessary when the

prescriber is requesting the multi-source brand drug due to a documented adverse reaction to the biosimilar; **AND**

B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
    1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. If the request is for brand Humira, at least two adalimumab biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
        ii. If the request is for brand Stelara, at least three ustekinumab biosimilars have been tried [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma); **OR**
    1. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    2. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and

Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are approved in the treatment of moderate to severe plaque psoriasis in adult patients. Otezla, a small-molecule therapy, is the only specialty agent approved for mild psoriasis, making it approved for psoriasis at any severity. As of July 2024, only apremilast (Otezla), etanercept (Enbrel), ixekizumab (Taltz), ustekinumab (Stelara), and secukinumab (Cosentyx) have been studied and approved for use in pediatric patients. Etanercept (Enbrel) is indicated in patients at least four years of age; apremilast (Otezla), ixekizumab (Taltz), ustekinumab (Stelara), and secukinumab (Cosentyx) are indicated in patients at least six years of age.

III. Adalimumab (Humira), apremilast (Otezla), brodalumab (Siliq), certolizumab (Cimzia), etanercept (Enbrel), ixekizumab (Taltz), guselkumab (Tremfya), risankizumab (Skyrizi), secukinumab (Cosentyx), and ustekinumab (Stelara) statistically significantly improves PASI by at least 90% in patients with moderate to severe plaque psoriasis compared to placebo.

IV. As of March 2021, there are four head-to-head trials that studied both induction and maintenance treatment, 14 head-to-head induction trials, and seven head-to-head maintenance trials published. Although head-to-head comparisons have shown statistical advantages for one product over another, the clinical meaningfulness of these differences remain unknown, and all products offer improvements in relevant outcomes with comparable safety profile.

- Induction and maintenance:
  i. The following agents statistically and significantly improve PASI by at least 90% compared to ustekinumab (Stelara): brodalumab (Siliq) with low certainty evidence; bimekizumab (Bimzelx), risankizumab (Skyrizi), and secukinumab (Cosentyx) with moderate certainty.
- Induction:
  i. The following agents statistically significantly improve PASI by at least 90% compared to adalimumab (Humira) with moderate certainty: guselkumab (Tremfya) and risankizumab (Skyrizi).
  ii. The following agents statistically and significantly improve PASI by at least 90% compared to etanercept (Enbrel) with moderate certainty: certolizumab (Cimzia), ixekizumab (Taltz), and ustekinumab (Stelara).
  iii. Ixekizumab (Taltz) statistically significantly improves PASI by at least 90% compared to ustekinumab (Stelara) with moderate certainty.
  iv. There is insufficient evidence to suggest that etanercept (Enbrel) is statistically inferior to apremilast (Otezla).
- Maintenance:
  i. Guselkumab (Tremfya) statistically significantly improves PASI by at least 90% compared to adalimumab (Humira) and secukinumab (Cosentyx) with moderate certainty.
  ii. Secukinumab (Cosentyx) statistically significantly improves PASI by at least 90% compared to etanercept (Enbrel) with low certainty.

V. **2019 American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) guidelines of care for the management and treatment of psoriasis with biologics:**

- "Majority of patients with mild to moderate disease (<10% BSA) are capable of adequately controlling disease solely with topical mediations or phototherapy."
- Guidelines define moderate psoriasis by 3 – 10% of the total body surface area involved and severe psoriasis is defined as ≥10% BSA involvement; however, psoriasis can be considered severe irrespective of BSA when it occurs in select locations (e.g., hands, feet, scalp, face, or genital area) or when it causes intractable pruritus.
- Biologics may be considered as monotherapy or in combination with other topical or systemic agents in patients with moderate to severe plaque psoriasis.
- Guidelines provide a Grade A recommendation for use of adalimumab (Humira), apremilast (Otezla), brodalumab (Siliq), etanercept (Enbrel), guselkumab (Tremfya), ixekizumab (Taltz), secukinumab (Cosentyx), and ustekinumab (Stelara) and a Grade B recommendation for risankizumab (Skyrizi) as a monotherapy treatment option in adult patients with moderate to severe plaque psoriasis. Guidelines were published in 2019 and precede the FDA-approval of risankizumab (Skyrizi); however, phase II and phase III risankizumab (Skyrizi)trials were available and included during guideline development.
- Guidelines have not provided recommendations for certolizumab (Cimzia) and bimekizumab (Bimzelx).
- Guidelines do not point to a specific agent or class when initiating treatment with a biologic. Primary failure is defined as those who are nonresponsive to initial biologic treatment whereas secondary failure represents those who initially respond but lose efficacy over time. Guidelines suggest primary failure to one agent does not preclude successful response to another agent under the same class; however, this may foretell reduced efficacy.
- Guidelines do not provide recommendations for switching therapies.
- Guidelines provide a Grade C recommendation indicating use for adalimumab (Humira), etanercept (Enbrel), or ustekinumab (Stelara) may be combined with apremilast (Otezla) to augment efficacy for the treatment of moderate to severe plaque psoriasis in adults when clinically indicated. This recommendation comes from consensus guidelines, opinion, case studies, or disease-oriented evidence. There is lack of patient-oriented evidence to support combination use with other biologics or other non-biologic specialty medications used to treat plaque psoriasis. Therefore, coverage for combination use with other biologics or other non-biologic specialty medications remains experimental and investigational.
- Mild to moderate psoriasis: Guidelines state that because psoriasis generally recurs after discontinuation of topical corticosteroid treatment, it is important to consider using steroid sparing agents that have been developed to supplement and reduce over-reliance on topical corticosteroids as monotherapy, decreasing the risk of corticosteroid adverse effects. Agents such as vitamin D analogues (Grade A recommendation), topical retinoids

(Grade B recommendation), and calcineurin inhibitors (Grade B recommendation) can be used as a maintenance treatment.

- As of January 2022, the guidelines have not been updated to place apremilast (Otezla) into a routine place of care in the treatment of mild to moderate psoriasis over the current guidelines of phototherapy, topical treatments, or a systemic DMARD.

VI. Coverage for the above agents in the setting of palmoplantar psoriasis (defined as psoriasis of the palms or soles presenting with hyperkeratotic, erythematous, plaques and fissures) may be appropriate when criteria for moderate-severe plaque psoriasis are met. Medical necessity for the treatment of guttate psoriasis and/or palmoplantar ***pustulosis*** are reviewed in the experimental and investigational section of this policy.

VII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

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IX. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar

product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Crohn's Disease

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), or ustekinumab-stba (Steqeyma)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   B. Diagnosis of **moderate to severe Crohn's disease; AND**
   C. Provider attestation or clinical documentation of at least one of the following:
      1. Treatment with systemic corticosteroids (e.g., prednisone, budesonide) has been ineffective, contraindicated, or not tolerated; **OR**
      2. Treatment with an immunomodulator (e.g., methotrexate, azathioprine, 6-mercaptopurine) has been ineffective, contraindicated, or not tolerated; **OR**
      3. Provider attestation or clinical documentation of high-risk disease (e.g., symptoms despite conventional therapy, obstruction, abscess, stricture, phlegmon, fistulas, resection, extensive bowel involvement, early age of onset, growth retardation)

II. **Certolizumab pegol (Cimzia), risankizumab (Skyrizi), guselkumab (Tremfya), non-preferred ustekinumab biosimilars, mirikizumab (Omvoh), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**

   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)] and ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)] have been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)) have been ineffective, contraindicated, or not tolerated; **AND**
      2. If the request is for non-preferred ustekinumab biosimilars, at least three preferred ustekinumab biosimilars [ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)],have been ineffective, contraindicated, or not tolerated.

III. **Vedolizumab SC (Entyvio) and infliximab-dyyb (Zymfentra)** are considered not medically necessary when used for all conditions, including but not limited to, maintenance of remission in Crohn's disease in place of intravenous (IV) formulation.
   A. Vedolizumab (Entyvio) subcutaneous (SC) formulation and infliximab-dyyb (Zymfentra) are considered not medically necessary when used for all indications, including but not limited to maintenance of remission in Crohn's disease. Intravenous (IV) formulation is clinically comparable in efficacy and safety to the subcutaneous (SC) formulation and is the

preferred product which can be accessed via the medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

IV. **Brand Humira or brand Stelara** may be considered medically necessary when the following criteria below are met:

A. Criteria I(A)-I(C) above are met; **AND**

B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**

C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. If the request is for brand Humira, treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
    ii. If the request is for brand Stelara, treatment with ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), AND ustekinumab-stba (Steqeyma) have been ineffective, contraindicated, or not tolerated; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)] and ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)].

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms; **AND**

IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat Crohn's disease or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Infliximab, etc.); **AND**

C. If the request is for **Brand Humira or Brand Stelara**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**

D. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. If the request is for brand Humira, at least two adalimumab biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
    ii. If the request is for brand Stelara, at least three ustekinumab biosimilars have been tried [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)]; **OR**

1. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**

2. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are FDA approved for the treatment of moderate to severe Crohn's disease (CD) based on safety and efficacy data from randomized-controlled trials. Certolizumab pegol (Cimzia), ustekinumab (Stelara), risankizumab (Skyrizi), infliximab-dyyb (Zymfentra), guselkumab (Tremfya), mirikizumab (Omvoh), and vedolizumab SC (Entyvio) are FDA-approved in adults only, while adalimumab (Humira) is approved in patients six years of age and older.

III. Diagnosis of CD is based on a combination of clinical presentation, endoscopic, radiologic, histologic, and pathologic findings that demonstrate inflammation of the luminal GI tract. As such, it is recommended that diagnosis is made by a provider specialized in detecting and treating inflammatory bowel diseases, such as a gastroenterologist.

IV. Therapeutic recommendations for patients with CD are established based upon disease location, disease severity, disease associated complications, and future disease prognosis. The goals of therapy are to induce remission, prevent relapse, and prevent the occurrence of disease complications, such as stricture and fistula.

Moderate to severe CD

V. According to the 2018 American College of Gastroenterology (ACG) guidelines patients with moderate to severe CD are considered to have failed to respond to treatment for mild to moderate disease, or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia. They have moderate to severely active endoscopic mucosal disease and disease activity corresponding to Crohn's Disease Activity Index (CDAI) score of 220-450.

VI. The symptoms of CD do not correlate well with the presence of active inflammation, and therefore should not be the sole guide for therapy. Objective evaluation by endoscopic imaging should be undertaken to avoid errors of under or overtreatment.

VII. Patients with CD are at risk of developing intestinal complications such as strictures, abscess, fistula, or phlegmon formation. According to the 2018 ACG guidelines features associated with high risk for progressive disease include age at diagnosis, initial extensive bowel involvement,

ileal/ileocolonic or proximal gastrointestinal (GI) involvement, perianal/severe rectal disease, and patients presenting with a penetrating or stenosis disease phenotype.

VIII. For patients with moderate to severe disease and those with moderate to high-risk disease, the 2018 ACG guidelines recommend treatment with oral corticosteroids used short term to induce remission (strong recommendation, moderate level of evidence). However, it is noted that one in five patients will become steroid refractory which is thought to be the result of unreliable efficacy in healing of the mucosa associated with steroids (weak recommendation, low level of evidence). Corticosteroids are also implicated in the development of perforating complications (abscess and fistula) and are relatively contraindicated in those patients. The 2021 American Gastroenterological Association (AGA) clinical guidelines make similar recommendations and suggest the use of corticosteroids in adult outpatients with moderate to severe CD over no treatment for induction of remission (conditional recommendation, moderate level of evidence).

IX. In patients with moderate to severe CD who remain symptomatic despite current or prior corticosteroid therapy, 2018 ACG guidelines recommend immunomodulators such as azathioprine, 6-mercaptopurine (strong recommendation, moderate level of evidence), and methotrexate (conditional recommendation, low level of evidence) to be effective for maintenance of remission. Due to slow time to clinical response that may not be evident for as long as 12 weeks, these agents are not recommended for short-term induction. The 2021 AGA guidelines make similar suggestions and recommend use of thiopurines over no treatment for the maintenance of remission (conditional recommendation, low level of evidence).

X. ACG guidelines recommend anti-TNF-alpha agents (infliximab [e.g., Remicade, Inflectra], adalimumab [Humira], certolizumab pegol [Cimzia]) in patients resistant to treatment with corticosteroids and refractory to thiopurines or methotrexate (strong recommendation, moderate level of evidence). Additionally, combination therapy of infliximab (e.g., Remicade, Inflectra) with immunomodulators (thiopurines) is more effective than treatment with either immunomodulators alone or infliximab (e.g., Remicade, Inflectra) alone in patients who are naïve to those agents (strong recommendation, high level of evidence). Recommendations are also made regarding the use of vedolizumab (Entyvio), natalizumab (Tysabri), and ustekinumab (Stelara) without preference for one biologic over the other. The AGA guidelines recommend early introduction of biologics with or without immunomodulators rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids; however, this recommendation is conditional with low certainty of evidence.

XI. Adalimumab (Humira), ustekinumab (Stelara), certolizumab (Cimzia), infliximab (e.g., Remicade, Inflectra), vedolizumab (Entyvio), natalizumab (Tysabri), risankizumab (Skyrizi), infliximab-dyyb (Zymfentra), mirikizumab (Omvoh), and guselkumab (Tremfya) have not been studied in head-to-head trials to compare the efficacy and safety between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by all biologic agents FDA approved for the treatment of moderate to severe CD in adults is incremental or better when evaluated against placebo.

XII. The timing of introduction of biologic agents is a matter of debate and more studies are needed to assess stepwise approach versus earlier administration of biologic agents in patients with moderate to severe disease. The 2019 British Society of Gastroenterology guidelines suggest that systemic corticosteroids are still an effective initial therapy for uncomplicated luminal moderate to severe disease, regardless of disease location; however, every effort should be made to limit exposure (strong recommendation, high-quality evidence). In patients with an aggressive disease course, or high risk, poor prognostic factors, early introduction of biologics may be considered (weak recommendation, moderate-quality evidence). High risk features include extensive disease, complex (stricturing or penetrating disease), perianal fistulizing disease, age under 40 years at diagnosis, and the need for steroids to control index flare; however, the predictive power of these features is limited.

High-risk/severe CD

XIII. Patients who are considered to have severe/fulminant disease are those with persistent symptoms despite the introduction of conventional corticosteroids or biologic agents as outpatients, or individuals presenting with high fevers, persistent vomiting, evidence of intestinal obstruction, significant peritoneal signs such as involuntary guarding or rebound tenderness, cachexia, or evidence of an abscess. They have endoscopic or radiographic evidence of severe mucosal disease and disease activity corresponding to CDAI score of >450.

XIV. Collective evidence suggests that initial treatment with biologics may be considered for patients with the following disease features: severe CD (CDAI >450, evidence of intestinal obstruction, abscess, stricture, or phlegmon, and endoscopic or radiographic evidence of severe mucosal disease such as deep ulcerations), perianal fistulizing disease, and pre- and post-operative CD. Additional consideration may be given to patients presenting with other poor prognostic factors (e.g., extensive bowel involvement, early age of onset) and should be evaluated on case-by-case basis.

Pediatric CD

XV. Children and adolescents with CD often present with a more complicated disease course compared to adult patients. Additionally, the potential impact of CD on growth, pubertal, and emotional development warrants a specific management strategy. The goals of therapy in pediatric CD are to relieve symptoms, achieve remission, optimize growth, and improve quality of life while minimizing drug toxicity.

XVI. Oral corticosteroids are recommended for inducing remission in children with moderate to severe active luminal CD. Corticosteroids should not be used as maintenance therapy. Thiopurines (azathioprine or 6-mercaptopurine) and methotrexate are recommended options for maintenance of steroid free remission in children at risk for poor disease outcomes. Methotrexate can be used as primary maintenance therapy or in thiopurine failure.

XVII. Anti-TNF-alpha therapy is recommended for inducing and maintaining remission in children with chronically active luminal CD despite prior optimized immunomodulator therapy or with active steroid-refractory disease. Anti-TNF-alpha therapy is recommended as primary induction and maintenance therapy for children with active perianal and fistulizing disease and can be considered for selected children with high risk for poor outcomes. According to ECCO/ESPGHAN clinical guidelines on the management of pediatric CD, early use of immunomodulators and

biologics warrants selection of ideal candidates who are at high risk for developing severe disease and depends on predictive factors. Predictive factors are largely the same as the ones for adults but further include the presence of marked growth retardation (>-2.5 height Z scores) and severe osteoporosis.

XVIII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XIX. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XX. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Ulcerative Colitis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), or ustekinumab-stba (Steqeyma)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   B. Diagnosis of **moderate to severe ulcerative colitis; AND**
   C. Provider attestation or clinical documentation of at least one of the following:
      1. Treatment with systemic corticosteroids (e.g., prednisone, budesonide) has been ineffective, contraindicated, or not tolerated; **OR**

2. Treatment with an immunomodulator (e.g., azathioprine, 6-mercaptopurine) has been ineffective, contraindicated, or not tolerated

II. **Golimumab (Simponi), ozanimod (Zeposia), mirikizumab (Omvoh), etrasimod (Velsipity), risankizumab (Skyrizi), guselkumab (Tremfya), non-preferred ustekinumab biosimilars, or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)] and ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)] has been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars (adalimumab -bwwd (Hadlima) and adalimumab -adaz (Adalimumab-ADAZ)) have been ineffective, contraindicated, or not tolerated; **OR**
      2. If the request is for non-preferred ustekinumab biosimilars, at least three preferred ustekinumab biosimilars [ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)] have been ineffective, contraindicated, or not tolerated.

III. **Vedolizumab SC (Entyvio) and infliximab-dyyb (Zymfentra)** are considered not medically necessary when used for all conditions, including but not limited to, maintenance of remission in ulcerative colitis in place of intravenous (IV) formulations.
   A. Vedolizumab (Entyvio) subcutaneous (SC) formulation and infliximab-dyyb (Zymfentra) are considered not medically necessary when used for all indications, including but not limited to maintenance of remission in ulcerative colitis. Intravenous (IV) formulations are clinically comparable in efficacy and safety to the SC formulations and are the preferred products which can be accessed via the medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

IV. **Brand Humira or brand Stelara** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**

i. If the request is for brand Humira, treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
ii. If the request is for brand Stelara, treatment with ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), AND ustekinumab-stba (Steqeyma) have been ineffective, contraindicated, or not tolerated; **OR**

2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
   i. Was life-threatening; **OR**
   ii. Required hospitalization; **OR**
   iii. Required intervention to prevent impairment or damage; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)] and ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)].

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat ulcerative colitis or another auto-immune condition (e.g., Remicade, Entyvio, Cimzia, etc.); **AND**
   A. If the request is for **Brand Humira or Brand Stelara**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
   B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. If the request is for brand Humira, at least two adalimumab biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima)and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
    ii. If the request is for brand Stelara, at least three ustekinumab biosimilars have been tried [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)]; **OR**
1. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
2. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are FDA approved in the treatment of moderate to severe ulcerative colitis (UC) in adult patients. As of May 2021, only adalimumab (Humira) has been FDA approved in moderate to severe ulcerative colitis in pediatric patients aged 5 years and older.

III. Adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), upadacitinib (Rinvoq), mirikizumab (Omvoh), etrasimod (Velsipity), infliximab-dyyb (Zymfentra), and risankizumab (Skyrizi) have not been evaluated in head-to-head trials to compare the efficacy and safety between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), upadacitinib (Rinvoq), mirikizumab (Omvoh), etrasimod (Velsipity), infliximab-dyyb (Zymfentra), and risankizumab (Skyrizi) is incremental or better when evaluated against placebo.

IV. Comparative efficacy and safety data are only available for vedolizumab (Entyvio) and adalimumab (Humira) at this time. There is low certainty that vedolizumab (Entyvio) has a comparable or better net health benefit compared to adalimumab (Humira) for induction and maintenance of clinical remission and mucosal healing in patients with moderate to severe UC. Vedolizumab (Entyvio) was found to be statistically superior with respect to certain efficacy outcomes; however, efficacy and safety is regarded as clinically comparable between the two agents.

V. The safety and efficacy of adalimumab (Humira) for the treatment of moderate to severe ulcerative colitis in pediatric patients aged five years and older was evaluated in one phase 3, double-blind, randomized, historical placebo controlled clinical trial (ENVISION-1). The trial included 93 patients, the majority of which were previously treated with corticosteroids and immunosuppressants at baseline and majority of patients (84%) were anti-TNF therapy naïve. Due to challenges with enrollment in the placebo arm, the trial underwent protocol amendments and was partially open label. The clinical trial studied two adalimumab (Humira) doses: 0.6 mg/kg every week (high dose) and 0.6 mg/kg every other week (standard dose). The two primary efficacy outcomes, Partial Mayo Score (PMS) and Full Mayo Score (FMS), were statistically significant against historical placebo in the high dose adalimumab (Humira) arm only, with 60% [95% CI: 44%-74%] of patients achieving PMS during induction and 45% [95% CI: 27%-64%] of patients achieving FMS during maintenance. During induction and maintenance phases, 22% and 37% of patients, respectively, experienced infections. There were 8% of patients which experienced serious infections, and 11% and 14% of patients experienced serious adverse events in the induction and maintenance phases, respectively.

VI. The 2019 American College of Gastroenterology (ACG) clinical guideline on the management of ulcerative colitis in adults recommend oral systemic corticosteroids for induction of remission in moderate to severe disease (strong recommendation, moderate quality of evidence). TNF inhibitors (adalimumab, golimumab, and infliximab), vedolizumab (Entyvio), and tofacitinib (Xeljanz) are also recommended for induction of remission (strong recommendation, moderate quality of evidence). For maintenance of remission, thiopurines are recommended if remission was achieved after corticosteroid induction (conditional recommendation, low quality of evidence). The guidelines note a systematic review of 1,632 patients with ulcerative colitis demonstrated that azathioprine and mercaptopurine had a 76% mean efficacy in maintaining remission. If remission was achieved with anti-TNF therapy, vedolizumab (Entyvio), or tofacitinib

(Xeljanz), clinical guidelines support continuing with the same agent to maintain remission (strong recommendation, moderate quality of evidence). The 2020 American Gastroenterology Association (AGA) guidelines make similar recommendations. Additionally, AGA recommends early use of biologic agents, rather than gradual step up after failure of 5-ASA in moderate to severe disease at high risk for colectomy. However, the overall quality of evidence supporting this recommendation was rated as very low. Guidelines also note that for patients with less severe disease, 5-ASA therapy may still be a reasonable choice of therapy to start with. For maintenance of remission, AGA makes no recommendation in favor of, or against, using biologic monotherapy, rather than thiopurine monotherapy due to absence of evidence.

VII. Patients who are primary non-responders to an anti-TNF therapy should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class. In patients with moderate to severe active ulcerative colitis who had an initial response but subsequently lost efficacy to one anti-TNF therapy, clinical guidelines recommend alternative anti-TNF therapy (but not the biosimilar to the original brand) compared with no treatment for induction of remission.

VIII. The 2018 European Crohn's and Colitis Organization and European Society of Pediatric Gastroenterology, Hepatology, and Nutrition clinical guidelines recommend treatment with oral systemic corticosteroids if patients are in the higher end of the moderate disease range and treatment with thiopurines for maintaining remission in children who are corticosteroid-dependent or relapsing frequently despite 5-ASA treatment, and 5-ASA intolerant patients. The guidelines recommend infliximab (e.g., Remicade, Inflectra) in chronically active or steroid-dependent ulcerative colitis, uncontrolled by 5-ASA and thiopurines, for both induction and maintenance of remission. Adalimumab (Humira) or golimumab (Simponi) could be considered in those who initially respond but then lose response or intolerant to infliximab (e.g., Remicade, Inflectra), based on serum levels and antibodies. Vedolizumab (Entyvio) should be considered in chronically active or steroid-dependent patients as second-line biologic therapy after anti-TNF failure.

IX. Vedolizumab SC (Entyvio) was studied in one Phase 3, randomized, placebo-controlled, double-blind, double-dummy trial (VISIBLE-1) against vedolizumab IV (Entyvio) and placebo for maintenance of UC remission. Before randomization, all patients in the trial first underwent induction treatment with vedolizumab IV (Entyvio) for two weeks. Those achieving response were randomized to maintenance treatment. At week 52, the primary endpoint, clinical remission, was achieved by 46.2% (36.5-56.2) of patients in the vedolizumab SC (Entyvio) arm, 42.6% (29.2-56.8) of patients in vedolizumab IV (Entyvio), and 14.3% (6.4-26.2) of patients in the placebo arm, with a statistically significant difference ($p<0.001$) between vedolizumab SC (Entyvio) and placebo. Secondary endpoints including endoscopic improvement and durable clinical response were also met with statistically significant difference between vedolizumab SC (Entyvio) and placebo. There were no new safety findings. Overall, vedolizumab (Entyvio) SC and IV formulations are clinically comparable when used to maintain UC remission in adults. Health plan considers continuation of therapy requests medically necessary provided that patients have achieved remission of disease using the IV formulation if vedolizumab (Entyvio) and are looking to switch to SC formulation of vedolizumab (Entyvio) for maintenance treatment.

X. In September 2024, guselkumab (Tremfya) was approved for adults with moderate to severe UC. For the treatment of UC, guselkumab (Tremfya) is administered as a 200 mg intravenous (IV) induction dose at Weeks 0, 4, and 8 followed by a maintenance dose of 100 mg subcutaneously (SC) at Week 16 and every 8 weeks thereafter, or 200 mg SC at Week 12 and every 4 weeks thereafter. This approval was based on the ongoing QUASAR trial, which included a Phase 2b dose-ranging induction study of IV guselkumab (Tremfya), confirmatory Phase 3 induction study, and a Phase 3 maintenance study. All participants had failed conventional therapies (thiopurines/corticosteroids) and 50% had failed two or more advanced therapies (i.e., TNF inhibitors, vedolizumab, tofacitinib). The primary endpoint of the Phase 2B IV portion of the trial was clinical remission measured at week 12, with the primary endpoint of the maintenance Phase 3 portion, sustained remission. A significantly greater proportion of patients in the guselkumab (Tremfya) group achieved clinical remission compared with those in the placebo group (22.6% vs 7.9%, respectively; adjusted treatment difference, 14.9%; $P<0.001$) at week 12; and, at week 44, 45.2% of patients on guselkumab (Tremfya) 100mg every 8 weeks, 50.0% on 200mg every 4 weeks, and 18.0% on placebo sustained remission. Adjusted treatment difference of 25.2%, *p<0.001* for 100mg and 29.5%, *p<0.001* for 200mg versus placebo. The largest number of ADE were COVID-19 infections and arthralgias (6.1% guselkumab [Tremfya] vs 6.8% placebo).

XI. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XII. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XIII. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of

death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Behcet's Disease (i.e., Behcet Syndrome)

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), or etanercept (Enbrel)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a specialist that is treatment this condition (e.g., rheumatologist, dermatologist, ophthalmologist, etc.); **AND (one of the following)**
      1. A diagnosis of recurrent **Behcet's Disease manifesting as oral ulcers of the mouth**; **AND**
         i. All of the following have been ineffective, not tolerated, or are contraindicated:
            a. Topical corticosteroids (e.g., triamcinolone) OR sucralfate mouthwash; **AND**
            b. Systemic therapy (e.g., colchicine, thalidomide, prednisone, benzathine penicillin); **OR**
      2. A diagnosis of **Behcet's disease manifesting as uveitis**; **AND**
         i. All of the following have been ineffective, not tolerated, or are contraindicated;
            a. Oral corticosteroids; **AND**
            b. At least one non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.).

II. **Apremilast (Otezla)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B1) above are met (i.e., apremilast [Otezla] would only be appropriate for Behcet's disease manifesting as oral ulcers of the mouth); **AND**

B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)] or etanercept (Enbrel) have been ineffective, contraindicated, or not tolerated.

III. **Non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], apremilast (Otezla), and etanercept (Enbrel) have been ineffective, contraindicated, or not tolerated

IV. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
         i. Treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
      2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
      3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **AND**
   B. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: apremilast (Otezla) and etanercept (Enbrel)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement of disease symptoms (reduction in inflammation, and/or lesions, reduction in amount of oral glucocorticoids needed, reduction in number of flares, etc.); **AND**

IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat Behcet's Disease or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Rinvoq, etc.); **AND**

   A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**

   B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

      1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
         i. Treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
      2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
      3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options

while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Adalimumab (Humira) and Etanercept (Enbrel) are not FDA-approved for the treatment of any manifestation of Behcet's Disease; however, several studies are available to support the use of these agents for various manifestations of the disease. Notably, mouth ulcers and ophthalmic complications. Examples are provided below.
    - Trial of etanercept in Behcet's Disease, double blind, placebo-controlled trial: 40 patients with mucocutaneous disease were enrolled in a trial evaluating etanercept compared to placebo. Results indicated efficacy of etanercept on oral ulcers, nodular lesions, papulopustular lesions, and had an increased probability of being ulcer and nodular lesion free compared to the placebo group. Although a small trial, the rarity of Behcet's Disease shall be taken into account.
    - A multicenter study of refractory Behcet's Disease treated with and-TNF alpha treatments was conducted: The trial included infliximab and adalimumab. These therapies resulted in an overall 90.4% response rate for all clinical manifestations, and specifically an 88% response rate for mucocutaneous manifestations and 96.3% for severe and/or refractory ocular disease. The incidence of flares was reduced during anti-TNF alpha treatment.
    - An analysis of published data in 369 patients using anti-TNF alpha agents for Behcet's Disease: This included peer-reviewed articles on Medline/PubMed and evaluated patients that were uncontrolled with or intolerant to other immunosuppressives. A rate of 90% clinical response was seen for the mucocutaneous manifestations of Behcet's disease, and a rate of 89% for ocular disease.

III. Behcet's Disease may manifest in many forms; however, it is commonly managed by rheumatology specialists; however, there may be instances when other inflammatory specialists may be managing and prescribing.

IV. Corticosteroids and oral DMARDS (typically azathioprine) have been mainstays of Behcet's Disease, with oral DMARDS having a particular role in ophthalmic manifestations.

V. For oral manifestations first line treatment is triamcinolone acetonide cream 0.1% in orabase, applied three to four times daily. High potency topical steroids may also be employed. Topical sucralfate may also be used with or as an alternative to topical corticosteroids. A strength of 1

gram/5 mL four times daily as a mouthwash is recommended to reduce pain, frequency, and healing time.

VI. In the latest 2018 EULAR recommendations in the treatment of Behcet's Disease, colchicine is used as the first-line treatment of mucocutaneous lesions. As well as benzathine penicillin, which is often added to colchicine to increase the effectiveness. Thalidomide is often helpful but should be used in caution in selected patients because of potential side effects. In acute and severe attacks of mucocutaneous lesions, oral corticosteroids can be used as an effective treatment. Additional other oral DMARDs (such as azathioprine) may be useful but are supported with less clinical evidence and are more case by case in nature of providing disease control or management.

VII. Apremilast (Otezla) was evaluated for Behcet's Disease in the following trial: Efficacy of apremilast for oral ulcers associated with active Behcet's Syndrome in a Phase III study. This indication was FDA-approved for treatment of oral ulcers of the mouth associated with Behcet's Disease in July 2019. A total of 207 patients were randomized to apremilast or placebo, and favorable treatment effect was noted. Although apremilast is an FDA-approved medication for Behcet's Disease, anti-TNF alpha therapies have equal or greater safety and efficacy data to support their use in this condition. Guidelines and key opinion leaders have consensus in regard to use of anti-TNF alpha therapies prior to use of apremilast; however, due to limited evidence of using one anti-TNF alpha agent after failure of another, trial of more than one agent is not required.

VIII. Standard dosing for adalimumab (Humira) is 40 mg every other week, and standard dosing for Etanercept (Enbrel) is 50 mg per week, either 25 mg twice weekly or 50 mg once weekly.

IX. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

X. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XI. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products

(the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Hidradenitis Suppurativa

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:

A. Member is being managed by, or in consultation with, a dermatologist; **AND**
B. A diagnosis of **hidradenitis suppurativa** when the following are met:
    1. Presence of inflammatory nodules and/or abscesses; **AND**
    2. Hurley Stage III (severe) disease; **OR**
    3. Hurley Stage II (moderate) disease with:
        i. Treatment with at least one oral antibiotic (i.e., doxycycline, minocycline, tetracycline, clindamycin/rifampin, etc.) has been ineffective, contraindicated, or not tolerated

II. **Bimekizumab (Bimzelx) or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(B) above are met; **AND**
B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)] and secukinumab (Cosentyx) have been ineffective, contraindicated, or not tolerated; **AND**
    1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars (adalimumab -bwwd (Hadlima) and adalimumab -adaz (Adalimumab-ADAZ)) have been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(B) above are met; **AND**
B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
    1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. Treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:

i. Was life-threatening; **OR**
ii. Required hospitalization; **OR**
iii. Required intervention to prevent impairment or damage; **AND**

B. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: secukinumab (Cosentyx)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in abscess and inflammatory nodule count, decrease in frequency of inflammatory lesions, etc.); **AND**
IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat hidradenitis suppurativa or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.); **AND**
   A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
   B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
         i. Treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
      2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
      3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**

iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, inflammatory disease affecting sweat glands characterized by recurrent, painful lesions that typically develop in intertriginous areas such as the axillae, groin, vulva, or gluteal cleft/anal region. Lesions usually start small and, over weeks to months, form into nodules, abscesses, or tunnels that can lead to scarring and fistulas overtime. The disease is classified in 3 clinical stages which help guide treatment: Hurley stage I (least severe), Hurley stage II (moderate severity), and Hurley stage III (most severe).

III. Adalimumab (Humira) is FDA-approved in patients in 12 years or older with moderate to severe HS supported by results of the PIONEER I and II RCTs.

IV. In the PIONEER studies, patients were only included if they had a diagnosis of Hurley Stage II or Hurley Stage III disease, had at least three inflammatory nodules/abscesses present at baseline, and had previously had an inadequate response to at least a 3-month trial of oral antibiotics. Adalimumab met the primary end point at week 12, where the Hidradenitis Suppurativa Clinical Response (HiSCR) primary efficacy endpoint (≥50 percent reduction in the total abscess and inflammatory nodule count with no increase in the abscess or draining sinus count) was achieved with adalimumab 40mg once weekly compared to the placebo groups. A three-year, open-label, extension study that followed the PIONEER trials suggests long-term efficacy and safety of adalimumab. The OLE study found a sustained rate of response (achievement of HiSCR) over time among patients who received 40 mg of adalimumab once weekly for at least 60 weeks. No new safety concerns were raised.

V. While oral antibiotics are frequently employed in moderate to severe disease as noted above, the data for these agents primarily stems from studies in patients with Hurley Stage I and II disease. Although the combination of clindamycin/rifampin has demonstrated improvement in terms of partial or total remission, only one small study with 10 patients has examined the use

in Hurley Stage III patients. Nearly 50% of patients in the PIONEER I and II studies of adalimumab had Hurley Stage III disease, and the randomized, controlled nature of the study provides greater assurance of efficacy for this more severe population than prior studies of oral antibiotics.

VI. Two phase 3, multicenter, double-blind, randomized, placebo-controlled trials (SUNSHINE and SUNRISE) evaluated the efficacy and safety of secukinumab (Cosentyx) in patients aged 18 years or older with a diagnosis of moderate to severe HS, defined as a total of five or more inflammatory lesions affecting two or more distinct anatomical areas. In both trials, this correlated to over 90 percent of participants having a diagnosis of Hurley Stage II or Hurley Stage III. Patients were randomized to secukinumab 300mg subQ every 2 weeks, every 4 weeks, or placebo. The primary endpoint evaluated the proportion of patients with a hidradenitis suppurative clinical response (HiSCR), defined as a decrease in abscess and inflammatory nodule count by 50% or more with no increase in the number of abscesses or in the number of draining fistulae compared with baseline at week 16. Key secondary endpoints include change in abscess and inflammatory nodule count, number of flares, and reduction in skin pain at week 16.
   - The primary endpoint was met in the SUNRISE trial, where 42% of participants on secukinumab every 2 weeks and 46% of those on secukinumab every 4 weeks achieved a clinically meaningful response in HiSCR, compared to 31% on placebo ($p<0.01$). In the SUNSHINE trial, the primary endpoint was not met in the secukinumab every 4 weeks, but secukinumab every 2 weeks achieved statistical and clinically significant change in HiSCR ($p=0.007$). Based on the results of the SUNSHINE trial, secukinumab every 2 weeks may be preferred over every 4 weeks dosing, especially in regard to the primary endpoint.
   - For the pooled secondary endpoints, only the SUNSHINE trial showed significantly fewer patients having flares in the secukinumab every 2 weeks group than in the placebo group during the first 16 weeks, while the SUNRISE trial showed significantly improved abscess and nodule count at week 16 in secukinumab every 4 weeks compared to placebo and statistically significant differences in the proportion of patients with flares between the secukinumab every 4 weeks group and the placebo group during the first 16 weeks. Both trials did show secukinumab improved patients' health-related quality of life (HRQoL) up to 52 weeks and many patients that did achieve a HiSCR at week 16 maintained their response at week 52.
   - No new safety concerns were raised in either trial.

VII. Two Phase 3, multicenter, double-blind, randomized, placebo-controlled trials (BE HEARD I and BE HEARD II) evaluated the efficacy and safety of bimekizumab (Bimzelx) in patients aged 18 years or older with a diagnosis of moderate to severe HS, defined as a total of five or more inflammatory lesions affecting two or more distinct anatomical areas. In both trials, participants had HS severity corresponding to Hurley Stage II or Hurley Stage III. The primary endpoint evaluated the proportion of patients with a hidradenitis suppurative clinical response (HiSCR50), defined as a decrease in abscess and inflammatory nodule count by 50% or more with no increase in the number of abscesses or in the number of draining fistulae compared with baseline at week 16. Key secondary endpoints included attainment of HiSCR75 response,

number of flares, change in the Dermatology Life Quality Index (DLQI) and reduction in skin pain at week 16.

- The primary endpoint was met in both trials at week 16, where 48% (BE HEARD I) and 52% (BE HEARD II) of participants on bimekizumab (Bimzelx) every 2 weeks achieved a clinically meaningful response in HiSCR50, compared to 29% (BE HEARD I) and 32% (BE HEARD II) on placebo ($p<0.006$; $p<0.003$, respectively).
- For secondary endpoints, HiSCR75 was statistically significant in both trials for the FDA approved dose. Incidence of flares was reported only in the BE HEARD II trial which did not meet statistical significance and was numerically higher in the bimekizumab (Bimzlex) arm than in placebo (29% vs 28%, $p=0.87$). HRQoL improvements were reported to be statistically and clinically meaningful at week 16 and skin pain response was numerically better with bimekizumab (Bimzelx) compared to placebo (32% vs 15%, $p=0.41$). Both trials showed that response was either higher or maintained at week 52.
- No new safety concerns were raised in either trial.

VIII. The Unites States and Canadian Hidradenitis Suppurativa Foundation 2019 guidelines provide recommendations for the treatment of HS. For mild-to-moderate HS, systemic antibiotics including tetracyclines are recommended as monotherapy and clindamycin and rifampin in combination is recommended in the second-line setting. For severe disease, clindamycin and rifampin may be used as a first line or adjunct treatment. For moderate-to-severe disease, moxifloxacin, metronidazole, and rifampin in combination are recommended as second- or third-line treatment. This recommendation is based on moderate-quality evidence from RCTs and one systemic review of retrospective and prospective studies. In moderate-to-severe disease when systemic antibiotics are ineffective or insufficient, the guidelines recommend the use of biologics, with a strong recommendation for adalimumab based on high quality evidence. Limited evidence is available for infliximab, anakinra, and ustekinumab with limitations including considerable variability and validity of end points, lack of dose ranging studies, and short follow-up periods. As of June 2023, the guidelines have not been updated with regard to place in therapy for secukinumab.

IX. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

X. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a

rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XI. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Uveitis and Panuveitis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima) or adalimumab-adaz (Adalimumab-ADAZ),** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, an ophthalmologist or rheumatologist; **AND**
   B. A diagnosis of **non-infectious intermediate, posterior, or panuveitis** when the following are met:
      1. Previous treatment with at least one periocular injection, implant, topical, or systemic corticosteroid (i.e., triamcinolone, dexamethasone, prednisone, fluocinolone, difluprednate, etc.) has been ineffective, contraindicated, or not tolerated; **AND**
      2. Previous treatment with at least one non-corticosteroid systemic immunomodulatory therapy (i.e., mycophenolate mofetil, tacrolimus, cyclosporine, azathioprine, or methotrexate) has been ineffective, contraindicated, or not tolerated.

II. **Non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ) has been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. Treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage

Renewal Evaluation

I. Member has exhibited improvement or stability of disease symptoms; **AND**
II. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat uveitis and panuveitis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.); **AND**
    A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
            i. Treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
        2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage(*as confirmed by a health plan pharmacist*); **OR**

3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Adalimumab (Humira) is FDA-approved for patients at least two years of age with non-infectious intermediate, posterior, or panuveitis based off data from the VISUAL I and II phase 3 RCTs.

III. The Fundamentals of Care for Uveitis (FOCUS) guideline recommends that the non-corticosteroid systemic immunomodulatory therapy (NCIST) agents listed above may be indicated for patients who have a failure or lack of tolerance to regional or systemic corticosteroids. Prior to initiation of alternative medications such as biologic agents, guidelines recommend dose escalation to the maximum tolerated/effective dose of NCIST. It is noted that use of biologic agents is supported for adalimumab, infliximab, and interferon alpha-2a.

IV. A meta-analysis published recently in 2018 supports this statement of biologic utility in uveitis. The analysis included 3 RCTs and 20 non-RCTs that examined adalimumab use in patients with non-infectious uveitis, with reduced time to treatment failure and improvements in visual acuity demonstrated.

V. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

VI. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

VII. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Giant Cell Arteritis

Initial Evaluation

I. **Tocilizumab-aazg (Tyenne)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **Giant Cell Arteritis (GCA)** when the following are met:
      1. Age at disease onset of at least 50 years; **AND**
         i. A positive temporal artery biopsy or halo sign on temporal artery ultrasound plus at least one of the following:
            a. New onset headache at time of diagnosis
            b. Morning stiffness in shoulders/neck
            c. Jaw or tongue claudication
            d. Scalp tenderness
            e. Temporary artery abnormality (tenderness to palpation or decreased pulsation)
            f. ESR ≥ 50 mm/hour or CRP ≥10 mg/liter
            g. Bilateral axillary involvement
            h. FDG-PET activity throughout the aorta
            i. Sudden vision loss; **OR**
         ii. At least three of the following:
            a. New onset headache at time of diagnosis
            b. Morning stiffness in shoulders/neck
            c. Jaw or tongue claudication
            d. Scalp tenderness
            e. Temporary artery abnormality (tenderness to palpation or decreased pulsation)
            f. ESR ≥ 50 mm/hour or CRP ≥10 mg/liter
            g. Bilateral axillary involvement
            h. FDG-PET activity throughout the aorta
            i. Sudden vision loss

II. **Brand Actemra** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**

B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
    1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. Treatment with tocilizumab-aazg (Tyenne) has been ineffective, not tolerated, or are contraindicated; **OR**
    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat giant cell arteritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.); **AND**
    - If the request is for **brand Actemra**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    - If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

i. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    1. Treatment with tocilizumab-aazg (Tyenne) have been ineffective, not tolerated, or are contraindicated; **OR**
ii. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
iii. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    1. Was life-threatening; **OR**
    2. Required hospitalization; **OR**
    3. Required intervention to prevent impairment or damage

Supporting Evidence

I. Giant cell arteritis (GCA) is an inflammatory vascular condition that is most frequently occurring in adult patients 50 years of age or older. It manifests with fever, fatigue, headache, transient or permanent vision loss, and large vessels involved like the aorta, and major vessels in upper extremities. Large vessel involvement includes dissections, aneurysm, tenderness to palpation, or asymmetric blood pressure. This condition is associated with elevated serum ESR and CRP levels and it is often closely related to polymyalgia rhematic disease.

II. Tocilizumab (Actemra) is FDA-approved for adult patients with giant cell arteritis based off results of a phase 3 RCT. In this trial, 251 patients were randomized to subcutaneous tocilizumab plus a prednisone taper or placebo plus a prednisone taper. The primary outcome of glucocorticoid-free remission statistically significant, with 53% and 56% (weekly and every other week dosing, respectively) of tocilizumab patients having sustained remission at week 52, compared to 14% and 18% (26-week versus 52-week taper, respectively) of prednisone patients ($p < 0.001$).

III. The 1990 ACR criteria for giant cell arteritis have been demonstrated to have a sensitivity of 93.5% and a specificity of 91.2%. Newer criteria were proposed in 2012 by a collaborative effort of EULAR/ACR that aimed to reduce the need for arterial biopsy. The newer criteria thus have a lower sensitivity (68%) and specificity (78%) and have not been officially endorsed by the ACR.

IV. In 2022 ACR/EULAR came out with updated classification criteria for giant cell arteritis. These criteria have demonstrated a sensitivity of 87% and a specificity of 94.8%. Current ACR guidelines are from 2021, therefore this new classification criteria is not included in the most current guidelines.

V. While not entirely clear at this time what long-term effects tocilizumab use has on the underlying pathophysiology and outcomes in giant cell arteritis patients, treatment to maintain remission may prevent potential adverse effects associated with long-term glucocorticoid use. Up to 50% of patients may experience return/relapse of giant cell arteritis after a tapering prednisone over one to two years. Glucocorticoids may be considered standard of care as first-line therapy and the primary treatment in patients presenting with giant cell arteritis. A guideline published by the British Society for Rheumatology (BSR)/British Health Professional in Rheumatology (BHPR) recommends that adjuvant therapy with methotrexate or other immunosuppressants be considered with recurrent relapses (started at the third relapse) or in patients who are unsuccessful with glucocorticoid taper.

VI. The 2021 American College of Rheumatology guidelines for GCA recommends starting high dose daily glucocorticoids, or tocilizumab with glucocorticoids or tocilizumab alone in newly diagnosed GCA. Patients with active extracranial large vessel involvement OR disease relapse with symptoms of cranial ischemia may start tocilizumab and glucocorticoids or start methotrexate with glucocorticoids if tocilizumab is not an option due to cost or tolerability. Guidelines have not been updated to include upadacitinib (Rinvoq).

VII. In a 2022 two-part study comparing new-onset compared to relapsing GCA treated with tocilizumab looking at 3-year timeline, 250 participants were randomized to receive tocilizumab weekly, tocilizumab every other week or placebo for 52 weeks (part 1), with a prednisone taper. In part two (open label), participants were treated at investigator discretion for 104 weeks. The primary endpoint in part 1 was the portion of patients achieving sustained glucocorticoid-free remission from week 12 to 52. In part two, the primary endpoint was maintenance of remission defined as absence of flare. A total of 250 participants completed part 1 and 215 participants transitioned to part 2. Of those, 184 patients (86%) were in clinical remission [TCZ QW, 81 (95%); TCW Q2W, 36 (90%); PBO, 67 (74%)] and stopped receiving blinded injections when they entered part 2. During part 2, 7 patients (3.3%) withdrew from the study for safety reasons, and 11 patients (5.1%) withdrew for non-safety reasons. Among the patients with new-onset disease, 49% in the TCZ QW group remained flare-free compared with 27% in the TCZ Q2W group and 28% in the PBO group. Participants with added tocilizumab experienced relapse after 575 (95% CI: 463) days. Whereas participants with glucocorticoids alone experienced relapse after 224 days (95% CI: 148, 322).

VIII. Tocilizumab can be used as initial treatment or as combination therapy with glucocorticoids in the first line setting. GCA is an emergent condition and patients diagnosed with GCA may be at great risk of sudden vision loss. Due to the urgency of the disease, patients are likely referred to seek urgent care and receive intravenous steroids to immediately reduce inflammation. Tocilizumab may be administered intravenously at point of care and patients may transition to subcutaneous injections thereafter.

IX. Upadacitinib (Rinvoq) is FDA approved for adults with GCA based off results of a Phase 3 RCT (SELECT-GCA). In this trial 428 patients were randomized to oral upadacitinib (Rinvoq) plus a prednisone taper or placebo plus a prednisone taper. The primary outcome of glucocorticoid-free remission was statistically significant, with 46% in the upadacitinib (Rinvoq)15 mg group

compared to 29% in the placebo group (17% treatment effect, p = 0.002). The safety profile of upadacitinib (Rinvoq) is similar to what is seen with other indications.

X. Although upadacitinib is an FDA-approved medication for GCA, tocilizumab (Actemra) has equal or greater safety and efficacy data to support its use in this condition. There are also no current head-to-head trials comparing upadacitinib (Rinvoq) to tocilizumab (Actemra) in GCA. Guidelines have consensus regarding the use of tocilizumab (Actemra); however, there is no consensus on the use of upadacitinib (Rinvoq) due to the newer approval.

XI. Standard dosing of upadacitinib (Rinvoq) for GCA is 15 mg once daily.

XII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XIII. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XIV. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Cryopyrin-Associated Periodic Syndromes (CAPS)

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of a **cryopyrin-associated periodic syndrome (CAPS), including neonatal-onset multisystem inflammatory disease (NOMID), familial cold autoinflammatory syndrome (FCAS) or Muckle-Wells syndrome (MWS); AND**
   C. Member has documented laboratory evidence of a genetic mutation in the Cold-Induced Auto-inflammatory Syndrome 1 (CIAS1), also known as NLRP

II. **Rilonacept (Arcalyst)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by or in consultation with a rheumatologist; **AND**
   B. A diagnosis of **CAPS, including FCAS or MWS**; **AND**
   C. Member has documented laboratory evidence of a genetic mutation in the Cold-Induced Auto-inflammatory Syndrome 1 (CIAS1), also known as NLRP3

Renewal Evaluation

I. Member has exhibited improvement or stability of disease symptoms; **AND**
II. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat cryopyrin-associated periodic syndromes (CAPS) or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Anakinra (Kineret) is FDA approved for the treatment of CAPS, particularly neonatal-onset multisystem inflammatory disease (NOMID). Anakinra is also frequently employed in the other CAPS, including Muckle-Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS), and can lead to rapid symptom improvement and a decrease in inflammatory markers. The pivotal trial in patients with NOMID was a single arm, prospective study that examined 43 patients treated with anakinra for up to 60 months. Outcomes included the use of a disease-specific symptom diary as well as reduction in inflammatory markers, with improvement seen in both. Eleven patients also went through a withdrawal phase, in which symptoms/inflammatory markers worsened, followed by response again when anakinra was reinitiated. A retrospective review of 22 patients with CAPS (varied phenotypes), demonstrated efficacy of anakinra. All 15 patients treated with anakinra achieved serologic remission and resolution of symptoms (fever, rash, conjunctivitis, and rheumatic symptoms). Other small, observational studies have demonstrated similar improvements both serologically and symptomatically in patients with MWS and FCAS.
II. Rilonacept (Arcalyst) is FDA approved for treatment of CAPS, particularly in patients 12 years of age and older with familial cold autoinflammatory syndrome (FCAS) or Muckle-Wells syndrome (MWS). The relevant phase III trials included 47 patients who were randomized to either weekly rilonacept or placebo, with the first trial analyzing efficacy within a six-week follow-up, and the second looking at response after withdrawal of the agent in the same population. Disease activity via symptom score (0-10 scale) was significantly reduced within a few days of onset (84% rilonacept vs 13% placebo), with a decrease in inflammatory markers also observed. No data is available for analysis in the NOMID population, and no head-to-head comparison with anakinra have been identified at this time.

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Recurrent Pericarditis

Initial Evaluation

I. **Rilonacept (Arcalyst)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a cardiologist; **AND**
   B. Member has a history of three or more episodes of pericarditis; **AND**
   C. Documentation that ALL of the following were ineffective, or all are contraindicated:
      1. NSAID
      2. colchicine
      3. corticosteroids

Renewal Evaluation

I. Member has exhibited improvement or stability of disease symptoms; **AND**
II. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Rilonacept (Arcalyst) is FDA approved for the treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and children 12 years of age and older.
II. According to the American College of Cardiology (ACC), pericarditis can be categorized as acute, incessant, recurrent, or chronic. An episode lasting ≥ 4-6 weeks without remission is defined to be incessant pericarditis, while pericarditis lasting > 3 months is defined to be chronic pericarditis. Key opinion leader input supports this classification and notes that for patients with an episode that appears to "recur" within 4 weeks is likely not a true recurrence but is still part of the initial episode or is incessant pericarditis.
III. The approval for this indication is based on findings from a phase III, multicenter, double-blind, event-driven, randomized-withdrawal design (RHAPSODY) trial (NCT03737110). Participants must have had at least one prior pericarditis episode meeting at least two of the following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation/PR-segment depression, or new/worsening pericardial effusion. During the 12-week run-in period,

participants received rilonacept (Arcalyst). Participants were then randomized 1:1 to monotherapy rilonacept (Arcalyst) versus placebo during the double-blind withdrawal period. A total of 86 patients were enrolled in the trial who predominantly had idiopathic pericarditis (85%) and only 15% had post–cardiac-injury pericarditis. In order for the trial to have 90% power to evaluate the primary efficacy endpoint, 22 recurrence events would be needed to detect a statistical significance. A total of 25 primary efficacy end-point events had accrued when the randomized-withdrawal period closed. The primary efficacy endpoint of the study was time to pericarditis recurrence; however, during the withdrawal period, there were too few recurrent events noted in the rilonacept (Arcalyst) group to allow for median time calculation. The median time to the first adjudicated recurrence in the placebo group was 8.6 weeks (95% CI, 4.0 to 11.7). One notable secondary endpoint was the proportion of participants who maintained clinical response at 16 weeks with 81% of the rilonacept group (95% CI; 58-95) compared to 20% (95% CI; 6-44) in the placebo group.

IV. According to key opinion leader input and available information from Kiniksa, the place in therapy for rilonacept (Arcalyst) is in recurrent pericarditis only. According to a Journal of American College of Cardiology (JACC) review on the management of acute and recurrent pericarditis, in acute pericarditis, the injury to the pericardium leads to a cascade of inflammatory process where IL-1 receptor (IL-1R) occupies a central role. In this process, IL-1α functions as an alarmin that is released during tissue injury and IL-1β gets released leading to amplification of the process. The rationale for the evaluation of rilonacept (Arcalyst) for recurrent pericarditis notes that this process is thought to stimulate the production of additional IL-1α and IL-1β which induces a self-perpetuating cycle of pericardial inflammation.

V. Both the 2015 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of pericardial diseases, and the 2020 American College of Cardiology review on the management of acute and recurrent pericarditis list treatment with NSAIDs/aspirin with colchicine for both acute pericarditis and recurrent pericarditis. According to ACC, anti-inflammatory therapy is the cornerstone of acute pericarditis. NSAIDs are recommended during an acute episode. Colchicine, which has a known anti-inflammatory effect, is recommended in patients with acute pericarditis in addition to aspirin or other NSAIDs. The benefit of colchicine is well established in both acute and recurrent pericarditis through various trials including, but not limited to, the CORE trial (2005), COPE trial (2005), and ICAP (2013). The ACC also notes that the efficacy of colchicine in recurrence has been shown in various studies. Key opinion leader input also supports the use of NSAIDs/aspirin and colchicine for both acute and recurrent pericarditis and that trial of these prior to rilonacept (Arcalyst) is clinically appropriate and aligns with evidence. Currently a 3-month course of colchicine is recommended for acute pericarditis; whereas, for recurrent pericarditis, a treatment course of at least 6 months is recommended.

VI. According to available information or guidelines for recurrent pericarditis, key opinion leader input and available data for the use of rilonacept (Arcalyst) in recurrent pericarditis, NSAIDs and colchicine (≥ 6 months) remain the standard of care for the treatment for initial recurrence of pericarditis. Low-dose corticosteroids are also often used in the treatment of recurrent pericarditis and are associated with a high treatment success rate per ACC. Currently, the place in therapy for rilonacept (Arcalyst) can be considered for patients with multiple recurrence of

pericarditis, and/or for patients where further use of NSAIDs, colchicine, and a low-dose corticosteroid are not clinically appropriate.

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Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

Initial Evaluation

I. **Tocilizumab-aazg (Tyenne)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a pulmonologist or rheumatologist; **AND**
   B. Tocilizumab-aazg (Tyenne) will not be used in combination with nintedanib (Ofev) or pirfenidone (Esbriet); **AND**
   C. A diagnosis of **Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)** when all of the following are met:
      1. The diagnosis is confirmed by a high resolution computed tomographic (HRCT) scan; **AND**
      2. Treatment with immunomodulators (e.g., mycophenolate mofetil or cyclophosphamide) has been ineffective, contraindicated, or not tolerated.

II. **Brand Actemra** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. Treatment with tocilizumab-aazg (Tyenne) have been ineffective, not tolerated, or are contraindicated; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Provider attests that member has exhibited improvement or stability of disease symptoms (e.g., sustained forced vital capacity (%FVC) decline or minimal decline in diffusing capacity of the lung for carbon monoxide (DLCO)); **AND**
    a. If the request is for **brand Actemra**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    b. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
        i. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused the patient to be unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
            1. Treatment with tocilizumab-aazg (Tyenne) have been ineffective, not tolerated, or are contraindicated; **OR**

ii. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**

iii. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:

1. Was life-threatening; **OR**
2. Required hospitalization; **OR**
3. Required intervention to prevent impairment or damage

Supporting Evidence

I. Scleroderma-associated interstitial lung disease (SSc-ILD) is a chronic lung disease in which fibrosis builds up in the lungs in a person diagnosed with systemic sclerosis (SSc). Direct pulmonary involvement in SSc is the main cause of death in patients with SSc. Early diagnosis, severity assessment, prediction of progression, and appropriate treatment of SSc- ILD is necessary to achieve the best possible patient outcomes. Goals of treatments include optimizing therapy, slowing disease progression, and prolonging time to progression and survival.

II. The presence of SSc-ILD is defined by the identification of fibrotic features on high- resolution CT (HRCT) scan. Surgical lung biopsy is seldom performed in SSc patients, unless the HRCT pattern is atypical, there is suspicion of a different diagnosis, or there is a complication such as cancer.

III. Pulmonary function tests (PFT) in patients with SSc-ILD demonstrate a restrictive pattern, with FVC and diffusion capacity of the lung for carbon monoxide (DLCO). DLCO is a measure of the conductance of gas transfer from inspired gas to the red blood cells. A low DLCO combined with reduced lung volumes suggests interstitial lung disease (ILD).

IV. Decisions to initiate or advance treatment often take into consideration the likelihood of progression, patient comorbidities, risk of toxicities, and current data on efficacy. Patients are treated based on expert-derived recommendations for the management of organ-specific manifestations. The European expert consensus published in 2020 recommends immunosuppressive therapies in severe or progressive ILD, including mycophenolate mofetil, cyclophosphamide, or nintedanib (Ofev) in patients requiring pharmacotherapy.

V. Nintedanib (Ofev) is approved to slow the rate of decline in pulmonary function in patients with SSc-ILD. Given its recent approval in 2019, its role in clinical practice (e.g., timing of initiation, use as add-on or monotherapy) for patients with SSc-ILD has not been well-defined.

VI. There is no evidence to suggest that combination therapy of tocilizumab (Actemra) and nintedanib (Ofev) or pirfenidone (Esbriet) will be safe or effective when used to treat Scc-ILD.

VII. The FDA has approved tocilizumab (Actemra) for slowing the rate of decline in pulmonary function in adult patients with SSc-ILD. The decision was based on the two clinical trials: the focuSSced Phase 3 trial and the Phase 2/3 faSScinate trial.

A. The focuSSed trial: A randomized, double-blind, placebo-controlled trial enrolled 212 participants >18 years of age to receive tocilizumab (Actemra) 145 mg subcutaneously once weekly (N=104) or placebo (N=106) for at least 48 weeks. Participants were excluded if they had severe restricted airway disease, including a percentage of predicted forced vital capacity (FVC% predicted) ≤ 55%, DLCO ≤45, or PAH WHO class 2 or higher. Patients were not on immunomodulating therapy (mycophenolate, cyclophosphamide) during enrollment.

   a. The primary endpoint, the difference in change from baseline in modified Rodnan skin score (mRSS), was not met. Post-hoc analyses were performed to evaluate results within the subgroups of participants with and without SSc-ILD. Results of the FVC secondary endpoints support the effectiveness of tocilizumab (Actemra) in reducing the rate of progressive loss of lung function in SSc-ILD.

	Overall population		Subgroup without SSc-ILD*		SSc-ILD subgroup*	
	Placebo	Tocilizumab	Placebo	Tocilizumab	Placebo	Tocilizumab
Number of patients	106	104	36	34	68	68
Change from baseline in mRSS score						
LSM	-4.41	-6.14	-6.16	-8.56	-3.77	-5.88
Difference in LSM (95% CI)†	-1.73 (-3.78, 0.32); p = 0.10		-2.40 (-5.59, 0.79)		-2.11 (-4.89, 0.67)	
Change from baseline in ppFVC (%)						
LSM	-4.58	-0.38	-0.82	-0.32	-6.40	0.07
Difference in LSM (95% CI)†	4.20 (2.00, 6.40); p=0.0002		0.50 (-2.27, 3.27)		6.47 (3.43, 9.50)	
Change from baseline in observed FVC (mL)						
LSM	-190	-24	-53	-11	-255	-14
Difference in LSM (95% CI)†	167 (83, 250); p = 0.0001		43 (-60, 145)		241 (124, 358)	

*Post-hoc results are shown for this subgroup. Four patients had ILD status missing at baseline.
†Difference in LSM (least means squared) between tocilizumab and placebo populations at week 48

   b. Subjects with SSc-ILD treated with tocilizumab (Actemra) had a smaller decline in mean ppFVC than placebo (0.07% vs. -6.4%, mean difference 6.47%), and a smaller decline in FVC compared to placebo (mean change -14mL vs. -255mL, mean difference 241mL).

B. The faSSinate trial was a randomized, double-blind, placebo-controlled trial which enrolled 87 participants > 18 years of age with SSc to receive tocilizumab (Actemra) 145 mg subcutaneously once weekly (N=44) or placebo (N=43). Participants were excluded if they had severe restricted airway disease, including a percentage of predicted forced vital capacity (FVC% predicted) ≤ 50%, DLCO ≤40, or PAH WHO class 2 or higher. Patients were not on immunomodulating therapy (mycophenolate, cyclophosphamide) during enrollment. The primary endpoint, the difference in change from baseline in modified Rodnan skin score (mRSS) at week 24, was not met. Results of the ad-hoc FVC secondary endpoints support the effectiveness of

tocilizumab (Actemra) in reducing the rate of progressive loss of lung function in SSc at week 48.

	ITT population	
	Placebo	Tocilizumab
mRSS change from baseline at week 48		
Number of patients	44	43
LSM	-2.10	-5.46
Difference in LSM (95% CI)	-3.36 (-7.3,0.32); p=0.0726	
Change from baseline in ppFVC (%) at week 48		
Number of patients	26	28
LSM	-6.31	-2.04
Difference in LSM (95% CI)	4.27 (0.68,7.78); p = 0.02	
Change from baseline in observed FVC (mL) at week 48		
Number of patients	27	28
LSM	-230	-91
Difference in LSM (95% CI)	138 (-2,279); p =0.05	

VIII. No new or unexpected safety findings were observed in both studies. Adverse events observed in subjects receiving tocilizumab (Actemra) were consistent with the known safety profile in other indications.

IX. The impact of tocilizumab (Actemra) on disease involvement in lung tissue as examined by CT scans has not been evaluated.

X. Safety and efficacy of tocilizumab (Actemra) in the setting of SSc-ILD has not been established in patients <18 years of age.

XI. Safety and efficacy of tocilizumab (Actemra) has not been established in other etiologies of ILD (e.g., idiopathic pulmonary fibrosis, non-specific interstitial pneumonia) and would remain experimental or investigational in non-SSc ILD.

XII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XIII. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XIV. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there

is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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Polymyalgia Rheumatica (PMR)

Initial Evaluation

I. **Sarilumab (Kevzara)** may be considered medically necessary when the following criteria are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **polymyalgia rheumatica** when the following are met:
      1. Presence of the following:
         I. Age at disease onset of at least 50 years; **AND**
         II. Presence of bilateral shoulder and/or pelvic girdle pain lasting at least 2 weeks; **AND**
         III. Presence of morning stiffness > 45 minutes; **AND**
         IV. Elevated CRP or ESR; **AND**
         V. Previous treatment with at least one glucocorticoid (i.e., prednisone, hydrocortisone, methylprednisolone, etc.) and attempted dose reduction/taper has been ineffective, contraindicated, or not tolerated

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., reduction of elevated inflammatory markers the CRP and ESR, improvement of bilateral shoulder and/or pelvic girdle pain, reduction of duration of daily morning stiffness)

Supporting Evidence

I. Sarilumab (Kevzara) is FDA-approved for adult patients with Polymyalgia rheumatica based off results of the SAPHYR study (n=118), a phase 3, randomized, double-blind placebo-controlled trial evaluating the efficacy of sarilumab in patients with PMR as assessed by the proportion of subjects with sustained remission for sarilumab with a shorter corticosteroid (CS) tapering regimen as compared to placebo with a longer CS tapering regimen. The duration was approximately 62 weeks which included a 4-week screening period, 52-week treatment period and 4-week follow-up period. Sustained remission rate was significantly higher in the sarilumab arm vs the placebo arm (28.3% vs 10.3%; P=0.0193). With regards to safety of sarilumab compared to placebo in the SAPHYR trial, more patients had adverse events in the sarilumab arm (94.9% vs 84.5% for sarilumab vs placebo), however, less patients experienced serious adverse events in the sarilumab arm when compared to placebo (20.7% vs 13.6%). The common adverse reactions occurring in ≥5% of patients treated with KEVZARA were neutropenia (15.3%), leukopenia (6.8%), constipation (6.8%), rash pruritic (5.1%), myalgia (6.8%), fatigue (5.1%), and injection site pruritus (5.1%).

II. The diagnosis and management of PMR requires detailed clinical examination. Given the complexities of diagnosis and treatment of this condition, supervision of treatment by a rheumatologist is required.

III. According to the European League Against Rheumatism/American College of Rheumatology Collaborative Initiative (EULAR/ACR) classification criteria for PMR, patients are required to be age 50 years and older to be considered for a diagnosis of PMR. The typical age of onset of the disease is 60-70 years old, and it is unlikely that a patient be diagnosed with PMR under the age of 50 years old. Other diagnoses should be considered and ruled out if a patient presents with symptoms under the age of 50. Additionally, the safety and efficacy of Kevzara in patients less than 50 years old have not been established in patients with PMR

IV. The presence of bilateral shoulder and/or hip pain are hallmark presenting symptoms for PMR. Within EULAR/ACR classification criteria for PMR and in the SAPHYR trial, bilateral shoulder and/or hip pain is required for diagnosis. Although morning stiffness is not mutually exclusive to PMR, the presence of morning stiffness for greater than > 45 minutes is very strong predictor of a PMR diagnosis and is commonly utilized in clinical practice.

V. Elevation of acute phase reactants such as CRP and/or ESR are strong predictors of diagnosis of PMR and are requirements for diagnosis within the EULAR/ACR classification criteria. All patients included in the SAPHYR trial must have had elevation in either CRP or ESR, defined as CRP> 10mg/L and/or ESR> 30mm/hour.

VI. Trial of a corticosteroid (e.g., prednisone) is considered first-line therapy and the standard of care for patients diagnosed with PMR. If patients exhibit a response/sustained remission with corticosteroids, a dose reduction or taper may be implemented to reduce long term exposure steroids. Sarilumab (Kevzara) is only indicated for patients who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper. Every patient within the SAPHYR trial were required to start prednisone and undergo a taper before starting sarilumab or placebo. The efficacy and safety of sarilumab in the first-line setting prior to corticosteroid use have not been established at this time.

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Investigational or Not Medically Necessary Uses

I. Cutaneous Sarcoidosis
   A. Apremilast and adalimumab have both been analyzed in this disease state. Efficacy data is limited to case reports and small studies at this time. One small RCT of adalimumab (n = 16) demonstrated a decrease in target lesion area compared to placebo. Similarly, a small observational study in 15 patients receiving apremilast demonstrated a reduction in induration at week 12 compared to baseline. Only one investigator performed the lesion assessment in this study, and similar to adalimumab, further larger scale, randomized studies are needed to fully establish efficacy of these agents.

II. Deficiency of IL-1 Receptor Antagonist (DIRA)
   A. Although anakinra (Kineret) is FDA approved for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA), the safety and efficacy data that led to FDA approval is considered to be of low quality. This approval is based on safety data from a National Institute of Allergy and Infectious Diseases (NIAID) study of nine patients with IL1RN mutations (17-I-0016). This study was neither designed nor powered to evaluate the efficacy of anakinra (Kineret) for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA). This study was part of a larger ongoing NIAID sponsored study on patients NOMID/CAPS, DIRA, CANDLE, SAVI, NLRC4-MAS, Still's Disease, and with other yet undifferentiated autoinflammatory diseases. This study is designed to identify the disease pathogenesis, including clinical, immunological, genetic and endocrinological characteristics of the disease. Currently, this indication is considered experimental and investigational due to the ongoing study and limited efficacy data for this indication.
   B. DIRA is a recently described recessively inherited autoinflammatory disease linked to activation of the IL-1 pathway. DIRA is to not be confused with DITRA (deficiency of interleukin-36 receptor antagonist) which usually results to generalized pustular psoriasis. Children with DIRA usually present with the following within the first weeks of life: symptoms of systemic inflammation (such as elevation of acute phase reactants and low-grade fever), pustular rashes, joint swelling, oral mucosal lesions and severe bone pain when being picked up. Currently, there are no other FDA approved agents approved for the treatment of DIRA. Patients who were evaluated in the NIAID sponsored study were

previously treated with antibiotics, NSAIDs, corticosteroids, IVIG, and DMARDs (e.g. methotrexate, azathioprine, etc).

III. Familial Mediterranean Fever
    A. Current studies for Familial Mediterranean Fever, a subgroup of periodic fever syndrome, are limited to case reports. In evaluating current evidence available, quantitative evaluation of response to biologic treatments (e.g., tocilizumab, infliximab, etanercept, adalimumab, anakinra and canakinumab) is difficult to obtain, and therefore, difficult to assess true efficacy and safety. In the absence of controlled studies to evaluate the safety and efficacy of biologics in the treatment of patients with Familial Mediterranean Fever, the use of biologics in this setting would be considered experimental and investigational.

IV. Graft Versus Host Disease (GVHD)
    A. A number of observational trials have examined etanercept in acute GVHD. Treatment regimens vary significantly between these observational studies. Data from a pilot and phase II trial pooled against observational data of standard of care patients receiving standard of care with steroids observed a higher complete response rate in those treated with etanercept. The results are significantly limited, however, by the observational, nonrandomized nature and thus prospective, randomized trials are needed to fully establish possible benefit in GVHD. The use of tocilizumab has also been studied in a small population (n = 8) with refractory GVHD. While response was observed in four of the six tocilizumab treated patients, the limited sample size is insufficient to confirm efficacy at this time.
    B. The safety and efficacy of the self-administered formulation of abatacept (Orencia) has not been evaluated. The intravenous form of abatacept (Orencia) is FDA-approved for the prevention or prophylaxis of acute graft vs. host disease (aGVHD). The FDA-approval of intravenous abatacept (Orencia) in aGVHD was based on two studies; a double-blind, placebo-controlled trial that showed survival benefit over placebo when used in combination with other immunosuppressive drugs; and a registry-based evaluation that compared patients that received abatacept (Orencia) in addition to conventional immunosuppressant therapy vs. conventional immunosuppressive therapy alone. The study observed to abatacept (Orencia) to have a survival benefit when used with conventional immunosuppressive treatments. The FDA-approved dose is 10 mg/kg IV over 60 minutes the day prior to stem cell transplantation, as well as days 5, 14, 28 days after transplantation, which conveniently overlaps with the expected inpatient stay following stem cell transplantation. Accurate dosing may only be achieved with the intravenous formulation. In addition to having unknown safety and efficacy, the self-administered formulation would have a greater injection burden, greater medication waste, and greater cost compared to the intravenous formulation. No other biologic therapies have been evaluated for this condition.

V. Grave's Ophthalmopathy
    A. A small phase III RCT (n = 32) analyzed tocilizumab use compared to placebo in this disease state. A statistically significant reduction was observed in the clinical activity score from baseline by week 16, but given the small sample size, the American Academy of

Ophthalmology has recommended that larger studies be completed to fully establish safety and efficacy for this indication.

VI. Guttate Psoriasis
    A. In this form of psoriasis, case reports suggest that the use of TNF inhibitors may induce flares when used. Typical treatment involves phototherapy and topical corticosteroids/vitamin D analogs, with tonsillectomy or antibiotics used for more refractory disease. There is no established efficacy data for the use of biologics or targeted DMARDs in this setting at this time.
VII. Interstitial Cystitis
    A. TNF inhibitors such as adalimumab and certolizumab pegol have been studied in small, phase III RCTs. In the study of certolizumab pegol, no difference was observed in interstitial cystitis compared to placebo at week 2. Secondary outcomes indicate benefit may occur in this population by week 10-18 of therapy. A similar study was completed with adalimumab, with no statistical difference observed in the primary outcome at week 12 compared to placebo. Further studies are needed to analyze efficacy in this population.
VIII. Lupus Nephritis and Systemic Lupus Erythematosus (SLE)
    A. Abatacept was analyzed in a large phase III RCT (n =695) in patients with lupus nephritis and in combination with mycophenolate and steroids. No difference was observed in the primary outcome of complete renal response at one year compared to placebo. Studies utilizing ustekinumab are currently recruiting in patients with SLE.
IX. Osteoarthritis
    A. Infliximab and adalimumab have been examined for use in patients with erosive, hand osteoarthritis. Mixed results have been seen so far. Open-label, observational studies of infliximab have shown potential benefit, while studies with adalimumab have been inconclusive. For instance, in a RCT of 60 patients, the difference in proportion of active disease in the adalimumab versus placebo group was not statistically significant. Further studies are needed to establish safety and efficacy.
X. Palmoplantaris **Pustulosis**/Pustulosis palmaris et plantaris
    A. It is not uncommon for forms of pustulosis to coexist with plaque psoriasis/psoriasis vulgaris; however, in absence of a covered indication and when associated criteria are met, use of non-biologic and biologic therapies in the setting of pustulosis is considered experimental and investigational.
    B. A small placebo-controlled (n =15) of etanercept in palmoplantaris pustolosis supported potential efficacy of TNF inhibitors. Observations have also occurred demonstrating worsening of this disease with use of TNF inhibitors. Other biologics, such as the use of IL-12/IL-23 inhibitor ustekinumab, did not demonstrate benefit in palmoplantaris pustolosis. A phase II study has analyzed guselkumab, and case reports of IL-1 inhibitors such as anakinra have been reported, though further study is needed to confirm the use of biologics in this population.
XI. Polymyositis and Dermatomyositis

A. One phase III trial is currently recruiting to analyze abatacept in patients with polymyositis and dermatomyositis. Anakinra has also been examined in a single group study (n = 15). Decrease in certain inflammatory markers was observed, however, the clinical and patient-centered outcomes of anakinra use in this population require further analysis. Another single-group, non-randomized trial (n = 13) looked at infliximab use in this population. None of the included patients had improvement in muscle strength by manual, and only two patients saw any improvement in disease activity scores.

XII. Pulmonary Sarcoidosis
   A. The TNF inhibitors infliximab, adalimumab, and etanercept have been studied to some extent in pulmonary sarcoidosis. A phase II study (n = 138) saw a statistically significant increase in functional vital capacity at week 24 compared to placebo, however, the effect size was small with a mean increase of just 2.5% from baseline. A small, open-label phase II study with etanercept was terminated early due to an excessive number of treatment failures. Case reports of adalimumab exist, and one study which examined 18 patients who switched after infliximab use saw improvement in just over one-third of patients, however, further prospective, randomized trials would be needed to fully establish safety and efficacy.

XIII. Pyoderma gangrenosum
   A. Case reports of the use of TNF inhibitors are available in this patient population. Most reports have involved patients with another indication for a TNF inhibitor, such as IBD or RA. A Phase III trial for this disease state is currently recruiting in Japan.

XIV. Sciatica
   A. One small RCT has examined adalimumab in patients with acute/severe radicular leg pain and imagine-confirmed lumber disc herniation. Of the 61 patients, a statistically significant, though small effect was seen at week 6 compared to placebo. At the 6 month follow up, the statistically significant difference was lost. While a difference in surgical discectomies was also seen,

XV. Systemic sclerosis (scleroderma)
   A. A phase III RCT (n =212) comparing tocilizumab to placebo in patients with systemic sclerosis did not observe a statistically significant difference in change from baseline to week 48 in the primary outcome in the Modified Rodnan Skin Score (mRSS).

XVI. Sjogren's Syndrome
   A. Studies with TNF inhibitors etanercept and infliximab have not demonstrated benefit in Sjogren's syndrome. A RCT (n = 103) found no difference in disease activity between infliximab and placebo by week 22. Likewise, a smaller RCT (n = 28) found no statistical difference with etanercept versus placebo at 12 weeks after treatment initiation. Small, open-label studies have also been done with abatacept, though sample size has been small, and data has been mixed, with one trial demonstrating improvement in salivary gland biopsy and extraglandular manifestations, and one showing no change in tear flow or improvement in other symptoms.

XVII. Wegener's Granulomatosis

A. One phase III RCT (n = 181) exists for the use of etanercept in patients with Wegener's Granulomatosis. Compared to standard of care (steroids plus cyclophosphamide or methotrexate), patient on etanercept demonstrated an initial sustained remission for at least six months that was not statistically different from standard of care. Likewise, a large proportion of patients lost response over the 27 months mean follow up period. An open-label study with infliximab (n = 16) has also been completed, with similar response rates to that described above in the etanercept study.

XVIII. Secukinumab in Rheumatoid Arthritis

A. Three phase III studies (NURTURE-1, REASSURE, REASSURE-2) evaluated the use of secukinumab in patients with rheumatoid arthritis. Novartis is not planning to pursue approval for secukinumab as the trials were terminated due to lack of comparative efficacy. Given the availability of other FDA approved options in this setting with established safety profiles and signals of efficacy, there is insufficient data to allow a standard path to coverage for Cosentyx in rheumatoid arthritis.

XIX. Vedolizumab Subcutaneous (Entyvio)

A. Vedolizumab (Entyvio) subcutaneous (SC) formulation is considered not medically necessary when used for all indications, including but not limited to maintenance of remission in ulcerative colitis. Intravenous (IV) vedolizumab (Entyvio) formulation is clinically comparable in efficacy and safety to the SC formulation and is the preferred product which can be accessed via the medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

XX. Infliximab-dyyb (Zymfentra)

A. Infliximab-dyyb (Zymfentra) is considered not medically necessary when used for all indications, including but not limited to maintenance of remission in ulcerative colitis and Crohn's disease. Intravenous (IV) infliximab formulation is clinically comparable in efficacy and safety to the SC formulation and is the preferred product which can be accessed via the medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy	Disease State
Systemic Janus Associated Kinase (JAK) Inhibitors in Chronic Inflammatory Disease Policy	Rheumatoid Arthritis
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)
	Psoriatic Arthritis
	Plaque Psoriasis
	Ankylosing Spondylitis
	Non-radiographic axial spondyloarthritis (nr-axSpA)
	Crohn's Disease
	Ulcerative Colitis
	Atopic Dermatitis
Multiple Sclerosis Policy	Multiple Sclerosis
nintedanib (Ofev); prifenidone (Esbriet)	Systemic sclerosis-associated interstitial lung disease (SSc-ILD)
tapinarof (Vtama)	Plaque Psoriasis
spesolimab SC (Spevigo)	Generalized pustular psoriasis (GPP)

Policy Implementation/Update

Action and Summary of Changes	Date
Live 07/01/2025: Addition of select ustekinumab biosimilars (Selarsdi, Steqeyma, and Yesintek) to preferred. Updated criteria for Systemic Juvenile Idiopathic Arthritis (SJIA) to prefer tocilizumab-aazg (Tyenne) and require anakinra (Kineret) to step through tocilizumab-aazg (Tyenne). Revised criteria for diagnosis of GCA.	06/2025
Updated indication table format	05/2025
Broke out non preferred biosimilars to be clearer on the requirement to t/f preferred biosimilars Added the following language, "…biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness"	03/2025
Addition of mirikizumab (Omvoh) for Crohn's Disease	03/2025
Removed age limits requirements. Addition of bimekizumab (Bimzelx) for the treatment of Hidradenitis Suppurativa and Psoriatic Arthritis. Addition of ustekinumab biosimilars (Steqeyma, Yesintek, Pyzchiva). Live 04/01/25: Addition of guselkumab (Tremfya) for Crohn's Disease	02/2025
Addition of ustekinumab biosimilar (Wezlana)	01/2025
Removed specialist requirement in mild to moderate plaque psoriasis for Otezla. Addition of certolizumab (Cimzia) to polyarticular juvenile idiopathic arthritis (pJIA). Addition of guselkumab (Tremfya) to ulcerative colitis (UC) for adults. Addition of bimekizumab (Bimzelx) to Ankylosing Spondylitis (AS) and Non-radiographic Axial Spondyloarthritis (nr-axSpA) criteria. Change to AS and nr-axSpA criteria to remove requirements for disease manifestation as axial or peripheral arthritis, change to definition of high disease activity, change to supportive evidence sections. Updated related policies.	11/2024
Addition of sarilumab (Kevzara) to polyarticular juvenile idiopathic arthritis (pJIA). Removed weight requirement for Taltz in pediatric plaque psoriasis. Updated Brand Actemra criteria to reflect MSB requirements to trial biosimilar Tyenne in both initial and renewal.	09/2024
Addition of risankizumab (Skyrizi) to ulcerative colitis policy	08/2024
Addition of tocilizumab (Tyenne) into policy as a preferred product. Addition of vedolizumab SC (Entyvio) to Crohn's disease policy requirements. Otezla age expansion in the setting of moderate to severe plaque psoriasis.	07/2024
Added Bimzelx to policy	04/2024
Updates in the setting of Behcet Syndrome, adding trial of etanercept (Enbrel) if requesting brand Humira. Change to ulcerative colitis criteria to require trial of at least one corticosteroid or immunomodulator; change to Crohn's disease criteria to require trial of at least one corticosteroid or immunomodulator and change to define high-risk Crohn's disease and remove severe Chron's disease	02/2024
Live 02/2024: removal of Skyrizi as a preferred product.	01/2024
Added vedolizumab SC (Entyvio) and infliximab-dyyb (Zymfentra) to policy for ulcerative colitis as not medically necessary when used for all indications. Updated Investigational or Not Medically Necessary Uses section to include vedolizumab SC (Entyvio) and infliximab-dyyb (Zymfentra). Added mirikizumab (Omvoh) to policy for ulcerative colitis indication. Updated supportive evidence section accordingly. Added etrasimod (Velsipity) to ulcerative colitis criteria.	01/2024
Live 02/01/2024: addition of select biosimilars (Hadlima and adalimumab-adaz) as preferred products, removal of brand Humira as a preferred product.	01/2024
Added age expansions for abatacept (Orencia) and etanercept (Enbrel) in psoriatic arthritis.	01/2024
Addition of new adalimumab biosimilars into policy.	07/2023
Live 12/2023: Updated criteria for hidradenitis suppurativa to include new line indication for Cosentyx. Updated supporting evidence and references.	06/2023
Added polymyalgia rheumatica indication for Sarilumab (Kevzara) with associated criteria and supporting evidence. Removed polymyalgia rheumatica from E/I section.	06/2023
Live 06/2023: Removed step criteria requiring trial of corticosteroids in giant cell arteritis. Added updated supporting evidence and updated guideline recommendations.	03/2023

Addition of adalimumab-atto (Amjevita) into policy.	02/2023
Updated supporting evidence and references for AS and nr-axSpA given approval for Rinvoq in nr-axSpA. Updated wording of renewal criteria regarding combination biologic use to reflect specific disease state referenced. Updated related policies section.	11/2022
Added Stelara age expansion in psoriatic arthritis to include members 6 years of age or older, formatting, and supporting evidence.	10/2022
Added Skyrizi to Crohn's disease criteria, updated supporting evidence section, updated formatting.	06/2022
Added ERA section and created criteria for use of Cosentyx as prompted by recent FDA approval. Updated PsA criteria to include expanded age for Cosentyx and new FDA approval for Skyrizi. Refined supporting evidence for PJIA and PsA to further clarify guidelines and treatment algorithm in pediatrics.	03/2022
Added criteria for Otezla to include line extension in setting of mild to moderate psoriasis with update to supporting evidence section. Updated PsA and AS formulary agents to include new line indications for Rinvoq and Xeljanz. Removed Behcet's oral corticosteroid requirement and updated to include systemic therapy to align more appropriately with guidelines. Updated Palmoplantar pustulosis E/I summary. Added Graft Vs. Host disease to E/I.	2/2022
Separated/removed JAK inhibitors (Xeljanz, Rinvoq, Olumiant) and created Systemic JAK Inhibitor Policy. Removed JAK inhibitors in E/I section and added Cosentyx in RA to E/I. Added Related Policies section.	12/2021
Removed criteria defining moderate to severe Crohn's disease, severe/fulminant Crohn's disease, and surgical Crohn's disease. Updated supporting evidence section accordingly.	09/2021
Added criteria for the treatment of systemic sclerosis-associated interstitial lung disease prompted by new FDA approval of Actemra for this indication.	08/2021
Updated Plaque Psoriasis, Cosentyx criteria to allow coverage in patients 6 six years of age or older; Updated policy to continue to steer to preferred products, Humira, Enbrel, Cosentyx, and Skyrizi	07/2021
Added criteria for treatment of recurrent pericarditis with Arcalyst	06/2021
Updated criteria for ulcerative colitis to include FDA approval of ozanimod (Zeposia) for adults with moderate to severe ulcerative colitis. Modified the weight requirement for Humira to a specific age group. Added a requirement to try and fail TNF blockers before allowing treatment with tofacitinib (Xeljanz) as recommended by FDA labeling. Supporting evidence and references updated.	06/2021
Updated criteria for ulcerative colitis to include FDA approval of adalimumab (Humira) for pediatric patients five years and older. Added the requirement for the documentation of member's current weight. Updated the language in the criterion requiring use of thiopurines only if corticosteroids were used to induce remission. Supporting evidence and references updated.	05/2021
Added DIRA indication as E/I for anakinra (Kineret); Updated the supporting evidence and references for plaque psoriasis.	04/2021
Updated PA policy to include FDA approvals for Xeljanz for PJIA. Updated supporting evidence section with clinical trial data	11/2020
Updated PA policy to include FDA approvals for Stelara and Taltz for plaque psoriasis in pediatric population. Updated supporting information section for plaque psoriasis to include clinical trial data supporting use of Stelara and Taltz in pediatric patients	09/2020
Updated the products for psoriatic arthritis to include guselkumab (Tremfya). Updated the supporting evidence section for psoriatic arthritis to reflect no changes in the guidelines with regard to guselkumab (Tremfya). Updated non-radiographic axial spondyloarthritis (nr-axSpA) criteria to include secukinumab (Cosentyx) and ixekizumab (Taltz). Updated nr-axSpA supporting evidence section to include trial information regarding new addition of secukinumab (Cosentyx) and ixekizumab (Taltz), as well as updated ACR guidelines.	08/2020
Removed Behçet syndrome from the E/I Section	02/2020
<u>Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis</u> • Added ixekizumab (Taltz) per new FDA indication <u>Cryopyrin-Associated Periodic Syndromes (CAPS)</u> • Added E/I information regarding Familial Mediterranean Fever	11/2019

Ulcerative Colitis • Added ustekinumab (Stelara) per FDA indication	

Criteria updated to new policy format. Specific changes include:
Rheumatoid Arthritis
• Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement
• Removed requirements for diagnosis due to varying methods to diagnose and limited value of this question from health plan standpoint
• Clarified use of oral DMARD requirement may be bypassed if all of them are contraindicated
• Added newly approved upadacitinib (Rinvoq) as a non-preferred alternative
Polyarticular Juvenile Idiopathic Arthritis (PJIA)
• Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement
• Added route to approval of Actemra as Actemra was previously in a separate policy
Systemic Juvenile Idiopathic Arthritis (SJIA)
• Separated SJIA from PJIA to have individual requirements
• Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement
• Updated route to approval to require trial of NSAIDs or indication member has severe active disease
• Routed therapy through anakinra (Kineret) over tocilizumab (Actemra) and abatacept (Orencia); followed by tocilizumab (Actemra) over abatacept (Orencia) as per
Psoriatic Arthritis
• Added requirement of the presence of active severe disease and provided specific indicators of severe disease
• Added clinical note: "If a patient has a diagnosis of both plaque psoriasis and psoriatic arthritis, approval of the requested medication can be made as long as the patient fulfills the criteria for at least one of the disease states and associated medication criteria."
Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis
• Removal of the requirement of DMARDs per the 2015 ACR guideline and 2016 ASAS/EULAR guideline
• Added requirement of a trial of two or more NSAIDS for an adequate trial of at least 4 weeks, also based on the above guidelines
• Added ixekizumab (Taltz) per new FDA indication
Plaque Psoriasis
• Clarified that moderate to severe disease is needed for payment consideration
• Clarified use of oral DMARD requirement may be bypassed if all are contraindicated
Crohn's Disease
• Added age requirement of six years of age or older
• Incorporated definition of moderate to severe Crohn's disease to help confirm disease severity
• Addition of breakdown to separate severe/fulminant Crohn's disease with definition to help confirm disease severity
  ○ Addition of IV corticosteroids as appropriate for this level of severity
• Addition of breakdown to Crohn's disease with surgical resection completed or planned
  ○ With further addition requiring presence of one additional factor demonstrating medical necessity of biologic treatment
Ulcerative Colitis
• Added age of 18 years or older
	08/2019

• Addition of trial of thiopurine for at least 8 weeks • Added ustekinumab (Stelara) per FDA indication <u>Behcet's Disease</u> • New indication added following approval of Otezla in this setting • Literature supports TNF therapy in oral and ophthalmic manifestations for Behcet's. A path to approval was added to the criteria • Otezla was added as a potential option after TNF have been found inefficacious or are contraindicated <u>Hidradentitis Suppurativa</u> • Updated prescriber language to be consistent with other sections • Added requirement of a trial of antibiotics for moderate disease <u>Uveitis/Panuveitis</u> • Added age of 2 years or older • Improved trial/fail wording to state "ineffective, contraindicated, or not tolerated" ○ No changes to trial and failure requirements <u>Giant Cell Arteritis (GCA)</u> • Added age of 18 years or older • Added criteria endorsed by guidelines to confirm diagnosis of GCA • Updated terminology around steroid use to require a previous trial with steroids rather than requiring concomitant steroid use with Actemra <u>Cryopyrin-Associated Periodic Syndromes (CAPS)</u> • Added requirement, of documented laboratory evidence of a genetic mutation	
Updated criteria to require trial and failure of Enbrel, Humira AND Cosentyx for Plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis	11/2018
Criteria update: Increased initial approval from 3 months to 6 months, updated initial QL to reflect 6 month approval duration. Added new Xeljanz IR 10mg tablet availability. Added baricitinib (Olumiant) as an option for the treatment of rheumatoid arthritis after trial and failure of a TNF antagonist.	07/2018
Criteria update: Added new Kevzara auto injector formulation, Xeljanz new indication in ulcerative colitis, added Cimzia new indication in plaque psoriasis, minor formatting edits.	06/2018
Criteria update: Align dosage and administration with quantity limit. Removal of the question pertaining to active infection.	02/2018
New Criteria Set – consolidated from all biologic agents along with Otezla and Xeljanz criteria sets. Within this new criteria set, here are the following updates: 1. 18 years of age requirement has been removed for Stelara as it has now been FDA approved for pediatric plaque psoriasis. 2. New FDA approved indication of psoriatic arthritis has been added for Xeljanz/Xeljanz XR and Taltz 3. The question regarding dual therapy has been refined to encompass the language of biologics and other non-biologics (e.g. Otezla and Xeljanz). 4. The question regarding DMARDs has been refined to only include agents that are administered non-biologic, non-specialty and that are administered orally. 5. For the indication of plaque psoriasis, the question addressing the trial of UVB has been combined with the trial of DMARDs.	01/2018