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

Medication	Indications
abatacept (Orencia®)	• Polyarticular Juvenile Idiopathic Arthritis • Psoriatic Arthritis • Rheumatoid Arthritis
adalimumab (Humira®)	• Ankylosing Spondylitis • Crohn's Disease • Hidradenitis Suppurativa • Polyarticular Juvenile Idiopathic Arthritis • Pediatric Crohn's Disease • Plaque Psoriasis • Psoriatic Arthritis • Ulcerative Colitis • Pediatric Ulcerative Colitis • Rheumatoid Arthritis • Uveitis/Panuveitis
anakinra (Kineret®)	• Cryopyrin-Associated Periodic Syndromes (CAPS) (including Chronic Infantile Neurological, Cutaneous and Articular Syndrome (CINCA) or Neonatal-Onset Multisystem Inflammatory Disease (NOMID)) • Rheumatoid Arthritis • Systemic Juvenile Idiopathic Arthritis (off-label)
apremilast (Otezla®)	• Plaque Psoriasis • Psoriatic Arthritis • Behcet Syndrome – ulcer of the mouth
brodalumab (Siliq®)	• Plaque Psoriasis
certolizumab (Cimzia®)	• Ankylosing Spondylitis

	• Crohn's Disease • Non-radiographic Axial Spondyloarthritis • Plaque Psoriasis • Psoriatic Arthritis • Rheumatoid Arthritis
etanercept (Enbrel®)	• Ankylosing Spondylitis • Plaque Psoriasis • Polyarticular Juvenile Idiopathic Arthritis • Psoriatic Arthritis • Rheumatoid Arthritis
golimumab (Simponi®/Simponi Aria®)	• Ankylosing Spondylitis • Psoriatic Arthritis • Rheumatoid Arthritis • Ulcerative Colitis
guselkumab (Tremfya®)	• Plaque Psoriasis • Psoriatic Arthritis
ixekizumab (Taltz®)	• Ankylosing Spondylitis • Non-radiographic Axial Spondyloarthritis • Adolescent Plaque Psoriasis • Plaque Psoriasis • Psoriatic Arthritis
rilonacept (Arcalyst®)	• Cryopyrin-Associated Periodic Syndromes (CAPS) (including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS))
risandizumab (Skyrizi®)	• Plaque Psoriasis • Psoriatic Arthritis • Crohn's Disease
sarilumab (Kevzara®)	• Rheumatoid Arthritis
secukinumab (Cosentyx®)	• Ankylosing Spondylitis • Non-radiographic Axial Spondyloarthritis • Plaque Psoriasis • Psoriatic Arthritis • Enthesitis-related arthritis
ustekinumab (Stelara®)	• Crohn's Disease • Adolescent Plaque Psoriasis • Plaque Psoriasis • Adolescent Psoriatic Arthritis • Psoriatic Arthritis • Ulcerative Colitis
tocilizumab (Actemra®)	• Giant Cell Arteritis

	• Polyarticular Juvenile Idiopathic Arthritis • Rheumatoid Arthritis • Systemic Juvenile Idiopathic Arthritis • Systemic Sclerosis-Associated Interstitial Lung Disease
ozanimod (Zeposia®)	• Ulcerative Colitis

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 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 (Humira) or etanercept (Enbrel)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. 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 tocilizumab (Actemra)** 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 (Humira) **AND** etanercept (Enbrel) have 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; **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.).

Supporting Evidence

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

III. 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 primary TNF non-responders have responded to other agents of the same mechanism of action.

References:

1. Fraenkel L, Bathon JM, England BR, et al. 2021 American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res*. 2021;73(7):924-939.

2. Alten R, Mischkewitz M. 2021 ACR guideline reflects changes in RA treatment. *Nat Rev Rheumatol*. 2021;17(9):513-514. doi:10.1038/s41584-021-00667-2
3. Van Vollenhoven, R. et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active-comparator-controlled trial. *Arthritis Rheumatol.* **72**, 1607–1620 (2020)
4. UpToDate, Inc. General principles and overview of management of rheumatoid arthritis in adults . UpToDate [database online]. Waltham, MA. Last updated October 18, 2021. Available at: http://www.uptodate.com/home/index.html.
5. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;**79:**685-699.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Initial Evaluation

I. **Adalimumab (Humira) or etanercept (Enbrel)** may be considered medically necessary when the following criteria below are met:
   A. Member is 2 years of age or older; **AND**
   B. Member is being managed by or in consultation with, a rheumatologist; **AND**
   C. 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) or tocilizumab (Actemra)** 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 (Humira) AND etanercept (Enbrel) have 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; **AND**
IV. Agent 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.)

Supporting Evidence

I. 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.

II. 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.

III. 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.

IV. 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.

References

1. UpToDate, Inc. Spondyloarthritis in children. UpToDate [database online]. Waltham, MA. Last updated December 4, 2020. Available at uptodate.com. Accessed February 4, 2022.
2. Ringold S, Angeles-han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care Res (Hoboken). 2019.
3. UpToDate, Inc. Polyarticular juvenile idiopathic arthritis: treatment. UpToDate [database online]. Waltham, MA. Last updated October 19, 2020. Available at: http://www.uptodate.com/home/index.html. Last accessed November 22 ,2021.
4. Brunner H, Ting T, el al. Tofacitinib in treatment of Polyarticular-course Juvenile idiopathic Arthritis: Results of a Phase 3 Randomized Double-blind Placebo withdrawal Study. ACR 2019. Abstract number: L22
5. Safety and Tolerability of Tofacitinib for Treatment of Polyarticular Course Juvenile Idiopathic Arthritis. 2020 [PROPEL Study] (NCT02592434)

Enthesitis-Related Arthritis (ERA)

Initial Evaluation

I. **Secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is 4 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. 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 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.

References

1. Ringold S, Angeles-han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. *Arthritis Care Res (Hoboken).* 2019;71(6):846-863.
2. Ruperto N, Foeldvari I, Alexeeva E, et al. Lb0004 efficacy and safety of secukinumab in enthesitis-related arthritis and juvenile psoriatic arthritis: primary results from a randomised, double-blind, placebo-controlled, treatment withdrawal, phase 3 study(Junipera). *Annals of the Rheumatic Diseases*. 2021;80(Suppl 1):201-202.
3. UpToDate, Inc. Spondyloarthritis in children. UpToDate [database online]. Waltham, MA. Last updated December 4, 2020. Available at uptodate.com. Accessed February 4, 2022.
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5. Horneff G, Burgos-Vargas R, Constantin T, et al. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (Week 12) of the CLIPPER study. *Ann Rheum Dis*. 2014;73(6):1114-1122.

Systemic Juvenile Idiopathic Arthritis (SJIA)

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is 2 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. 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. **Tocilizumab (Actemra)** 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 anakinra (Kineret) 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(C) above are met; **AND**
   B. Treatment with anakinra (Kineret) AND tocilizumab (Actemra) 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; **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.)

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).

References

1. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum*. 2013;65(10):2499-2512.
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5. Quartier P, Allantaz F, Cimaz R, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis.* 2011;70(5):747-754.
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Psoriatic Arthritis

Initial Evaluation

I. **Adalimumab (Humira), etanercept (Enbrel), secukinumab (Cosentyx), or risankizumab (Skyrizi)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **OR**
      1. Member is two years of age or older and the request is for secukinumab (Cosentyx); **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist or dermatologist; **AND**
   C. 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 CRP or 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), ustekinumab (Stelara), apremilast (Otezla), or guselkumab (Tremfya)** 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 (Humira), etanercept (Enbrel), secukinumab (Cosentyx), AND risankizumab (Skyrizi) have been ineffective, contraindicated, or not tolerated; **AND**
   C. The member is 18 years of age or older, if prescribed abatacept (Orencia), certolizumab (Cimzia), golimumab (Simponi), ixekizumab (Taltz), apremilast (Otezla), or guselkumab (Tremfya); **OR**
   D. If request is for ustekinumab (Stelara); **AND**
      1. The member is 6 years of age or older.

**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.)

Supporting Evidence

I. 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.
II. 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.
III. 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 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.

IV. 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).

V. 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.

VI. 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).

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Ankylosing Spondylitis

Initial Evaluation

I. **Adalimumab (Humira)**, **etanercept (Enbrel)**, **or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **ankylosing spondylitis** when the following are met:
      1. High disease activity as indicated by BASDAI score of at least 4 or ASDAS score of at least 2.1; **AND**
      2. Treatment with at least two different NSAIDs (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated; **AND**
      3. Disease manifested as axial disease; **OR**
      4. Disease manifested as peripheral arthritis.

II. **Certolizumab (Cimzia), ixekizumab (Taltz), and golimumab (Simponi)** 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 (Humira), etanercept (Enbrel), AND secukinumab (Cosentyx) have 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; **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.)

Supporting Evidence

I. The above agents are approved for adult patients in the treatment of ankylosing spondylitis based on safety and efficacy data from randomized-controlled trials.
II. The 2019 ACR/SAA/SPARTAN guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% responding). For those patients with inadequate response despite continuous NSAID treatment, the panel strongly recommends use of TNF inhibitors. For those patients with continued active disease, the panel conditionally recommends trial of a different TNF inhibitor over treatment with a non-TNF inhibitor biologic. Observational studies have demonstrated clinical improvement in patients who have switched TNF inhibitors compared to switching to a DMARD or non-TNF biologic.
III. The ACR/SAA/SPARTAN guideline conditionally recommends against the use of DMARDs in patients with ankylosing spondylitis that remains active despite NSAID treatment. 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.
IV. The 2022 ASAS/EULAR guidelines for the treatment of axial spondyloarthritis (axSpA) reference the use of JAK inhibitors in the treatment algorithm. The term axial spondyloarthritis (axSpA), encompasses both active ankylosing spondylitis (or radiographic AS) and nr-axSpA as one entity part of the same chronic inflammatory musculoskeletal spectrum with similar clinical presentations, comorbidities, disease burden, and treatment response. ASAS/EULAR recommends patients try and fail at least 2 NSAIDs over 4 weeks as first line therapy and treat local musculoskeletal inflammation with glucocorticoid injection; sulfasalazine may be considered in patients with peripheral symptoms, however use of conventional non-biologic DMARDS (e.g. sulfasalazine, leflunomide, methotrexate, etc.) is not recommended in axial disease. In contrast to ACR/SAA/SPARTAN, ASAS/EULAR guidelines highly recommend treatment with a TNF inhibitor, IL-17 inhibitor, or JAK inhibitor for patients with high disease activity, defined by a BASDAI of at least 4 or an ASDAS of at least 2.1, despite conventional treatment with NSAIDS. Starting with a TNF inhibitor or IL-17 inhibitor is preferred clinically, given long term data for use of JAK inhibitors in axSpA is still missing. 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.

V. Although specific JAK inhibitors were not referenced in the ASAS/EULAR guideline, 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 RA, reflective of a JAK inhibitor class effect, or specific to tofacitinib. Until more data become available, ASAS/EULAR advises 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.

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Non-radiographic Axial Spondyloarthritis

Initial Evaluation

I. **Adalimumab (Humira), etanercept (Enbrel), or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **non-radiographic axial spondyloarthritis** when the following are met:
      1. High disease activity as indicated by BASDAI score of at least 4 or ASDAS score of at least 2.1; **AND**

2. Treatment with at least two different NSAIDs (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated; **AND**
3. Disease manifested as axial disease; **OR**
4. Disease manifested as peripheral arthritis.

II. **Certolizumab (Cimzia) or ixekizumab (Taltz)** 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 (Humira), etanercept (Enbrel), AND secukinumab (Cosentyx) 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; **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.)

Supporting Evidence

I. Currently, certolizumab pegol, ixekizumab, secukinumab, and upadacitinib are the only FDA approved agent for adults with non-radiographic axial spondyloarthritis. 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.
II. A phase 3 double-blind, randomized, placebo-controlled trial (C-AXSPAND) examined the use of certolizumab pegol in patients with non-radiographic axial spondyloarthritis who had an inadequate response to at least two prior NSAIDs. In terms of the primary endpoint of patients achieving a response in the Ankylosing Spondylitis Disease Activity Score-Major Improvement (ASDAS-MI) at week 52, a significantly more patients in the certolizumab pegol group achieved

this clinical response compared to placebo (47% vs 7%, OR 15.2, 95% CI 7.3 to 31.6). Improvement was also seen in secondary outcomes such as quality of life questionnaires.

III. A phase 3, double-blind, randomized, parallel-group, placebo-controlled trial (COAST-X) assessed the use of ixekizumab in patients with non-radiographic axial spondyloarthritis who had an inadequate response to at least two prior NSAIDs. Primary endpoint of Assessment of Spondyloarthritis International Society 40 (ASAS40) response at weeks 16 and 52 on ixekizumab 80 mg every four weeks compared to placebo was achieved (week 16: 35% vs 19%, OR 2.36, 95% CI 1.23-4.51, p=0.0094, and week 52: 30% vs 13%, OR 2.82, 95% CI 1.38-5.77, p=0.0045). Improvement was also seen in secondary outcomes such as Ankylosing Spondylitis Disease Activity Score (ASDAS) and quality of life.

IV. A phase 3, double-blind, randomized, placebo-controlled trial (PREVENT) assessed the use of secukinumab in patients with non-radiographic axial spondyloarthritis who had active disease (BASDAI greater or equal to four, visual analogue scale (VAS) for total back pain greater or equal to 40) despite NSAID therapy. Primary endpoints of Assessment of Spondyloarthritis International Society 40 (ASAS40) response at week 16 in TNFi-naïve patients on secukinumab 150 mg with loading dose compared to placebo and ASAS40 response at week 52 in TNFi-naïve patients on secukinumab 150 mg without loading dose compared to placebo were achieved (week 16: 41.5% vs 29.2%, p=0.0197, and week 52: 39.8% vs 19.9%, p<0.0021). Improvement was seen in secondary outcomes at week 16 for Ankylosing Spondylitis Disease Activity Score (ASDAS) and quality of life.

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. The 2022 ASAS/EULAR guidelines for the treatment of axial spondyloarthritis (axSpA) reference the use of JAK inhibitors in the treatment algorithm. The term axial spondyloarthritis (axSpA), encompasses both active ankylosing spondylitis (or radiographic AS) and nr-axSpA as one entity part of the same chronic inflammatory musculoskeletal spectrum with similar clinical presentations, comorbidities, disease burden, and treatment response. ASAS/EULAR recommends patients try and fail at least 2 NSAIDs over 4 weeks as first line therapy and treat local musculoskeletal inflammation with glucocorticoid injection; sulfasalazine may be considered in patients with peripheral symptoms, however use of conventional non-biologic DMARDS (e.g. sulfasalazine, leflunomide, methotrexate, etc.) is not recommended in axial

disease. In contrast to ACR/SAA/SPARTAN, ASAS/EULAR guidelines highly recommend treatment with a TNF inhibitor, IL-17 inhibitor, or JAK inhibitor for patients with high disease activity, defined by a BASDAI of at least 4 or an ASDAS of at least 2.1, despite conventional treatment with NSAIDS. Starting with a TNF inhibitor or IL-17 inhibitor is preferred clinically, given long term data for use of JAK inhibitors in axSpA is still missing. 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 can be considered.

VII. Although specific JAK inhibitors were not referenced in the ASAS/EULAR guideline, 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 RA, reflective of a JAK inhibitor class effect, or specific to tofacitinib. Until more data become available, ASAS/EULAR advises 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. \

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Plaque Psoriasis

Initial Evaluation

I. **Adalimumab (Humira), etanercept (Enbrel), secukinumab (Cosentyx), or risankizumab (Skyrizi)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older if prescribed adalimumab (Humira) or risankizumab (Skyrizi); **OR**
      1. Member is 4 years of age or older if prescribed etanercept (Enbrel); **OR**
      2. Member is 6 years of age or older if prescribed secukinumab (Cosentyx); **AND**
   B. Member is being managed by or in consultation with a dermatologist; **AND**
   C. 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), and ustekinumab (Stelara)** 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 (Humira), etanercept (Enbrel), secukinumab (Cosentyx) AND risankizumab (Skyrizi) have been ineffective, contraindicated, or not tolerated; **AND**
   C. The member is 18 years of age or older, if prescribed apremilast (Otezla), brodalumab (Siliq), certolizumab (Cimzia), or guselkumab (Tremfya); **OR**
   D. The request is for ustekinumab (Stelara); **AND**
      1. The member is 6 years of age or older; **OR**
   E. The request is for ixekizumab (Taltz); **AND**
      1. Member is 6 years of age or older; **AND**
      2. Member has a body weight > 50 kg (110 lb)

III. **Apremilast (Otezla)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a dermatologist; **AND**
   C. 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 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. 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**
    ii. 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**
    iii. Treatment with adalimumab (Humira), etanercept (Enbrel), secukinumab (Cosentyx) AND risankizumab (Skyrizi) have 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; **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.)

Supporting Evidence

I. 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 May 2021, only 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; ixekizumab (Taltz), ustekinumab (Stelara), and secukinumab (Cosentyx) are indicated in patients at least six years of age.

II. 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.

III. 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 (investigational), 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.

IV. **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 is 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 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; however, phase II and phase III risankizumab trials were available and included during guideline development.
- Guidelines have not provided recommendations for certolizumab (Cimzia).
- 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.

V. 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.

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Crohn's Disease

Initial Evaluation

I. **Adalimumab (Humira) or risankizumab (Skyrizi)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **OR**
   B. Member is 6 to 17 years of age and the request is for **adalimumab (Humira); AND**
      1. Documentation of member's current weight is provided; **AND**
   C. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   D. Documentation member has **severe Crohn's disease; OR**
   E. Documentation member has **moderate to severe Crohn's disease** when the following are met:
      1. Treatment with oral corticosteroids (e.g., prednisone, methylprednisolone) used short-term to induce remission or alleviate signs/symptoms of disease flare has been ineffective, contraindicated, or not tolerated; **AND**
      2. Treatment with at least one immunomodulatory agent (e.g., methotrexate, azathioprine, 6-mercaptopurine) over an eight-week period to maintain remission has been ineffective, contraindicated, or not tolerated; **OR**

II. **Certolizumab pegol (Cimzia) or ustekinumab (Stelara)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(C)-I(E) above are met; **AND**
   B. Member is 18 years of age or older; **AND**
   C. Treatment with adalimumab (Humira) AND risankizumab (Skyrizi) 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; **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.)

Supporting Evidence

I. 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) and risankizumab (Skyrizi) are FDA-approved in adults only, while adalimumab (Humira) is approved in patients six years of age and older.

II. 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.

III. 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 occurrence of disease complications, such as stricture and fistula.

Moderate to severe CD

IV. 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.

V. Symptoms of CD do not correlate well with 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.

VI. 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.

VII. 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).

VIII. 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).

IX. 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.

X. Adalimumab (Humira), ustekinumab (Stelara), certolizumab (Cimzia), infliximab (e.g., Remicade, Inflectra), vedolizumab (Entyvio), natalizumab (Tysabri), and risankizumab (Skyrizi) 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.

XI. 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.

Severe CD

XII. Patients who are considered to have severe/fulminant disease are those with persistent symptoms despite 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.

XIII. 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

XIV. Children and adolescents with CD often present with a more complicated disease course compared to adult patients. Additionally, 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.

XV. 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.

XVI. 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.

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Ulcerative Colitis

Initial Evaluation

I. **Adalimumab (Humira)** may be considered medically necessary when the following criteria below are met:
   A. Member is 5-17 years of age; **AND**
      1. Documentation of member's current weight is provided; **OR**
   B. Member is 18 years of age or older; **AND**
   C. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   D. A diagnosis of **moderate to severe ulcerative colitis** when the following are met:
      1. Previous treatment with at least one systemic corticosteroid (e.g., budesonide, prednisone, hydrocortisone, methylprednisolone, etc.) has been ineffective to induce remission, is contraindicated, or is not tolerated; **AND**
      2. If systemic corticosteroids were used to induce remission, previous treatment with at least one thiopurine (azathioprine or 6-mercaptopurine) over an eight-week period to maintain remission has been ineffective, contraindicated, or not tolerated.

II. **Golimumab (Simponi), ustekinumab (Stelara), or ozanimod (Zeposia)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(B)-I(D) above are met; **AND**
   B. Treatment with adalimumab (Humira) 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; **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.)

Supporting Evidence

I. 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.
II. Adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), golimumab (Simponi), and ozanimod (Zeposia) 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), and golimumab (Simponi) is incremental or better when evaluated against placebo. There is moderate certainty that ozanimod (Zeposia) provides promising but inconclusive net health benefit compared to placebo in patients with moderate to severe UC due to evidence being available from only one phase 3 trial and less established safety data compared to other UC treatment options.
III. 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.

IV. 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, 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.

V. 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, 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.

VI. 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.

VII. 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.

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

Initial Evaluation

I. **Adalimumab (Humira) or etanercept (Enbrel)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. 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 (Humira) or etanercept (Enbrel) have 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 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.)

Supporting Evidence

I. 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.

II. 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.

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

IV. 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.

V. 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.

VI. 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.

VII. 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.

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Hidradenitis Suppurativa

Initial Evaluation

I. **Adalimumab (Humira)** may be considered medically necessary when the following criteria below are met:
   A. Member is 12 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a dermatologist; **AND**
   C. 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

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 hidradenitis suppurativa or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Adalimumab (Humira) is FDA-approved for HS in patients in 12 years or older with moderate to severe disease based off results of the PIONEER I and II RCTs.
II. 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. This mirrors the recent evidence-based guidelines published by the British Association of Dermatologists which recommends adalimumab use be reserved for patients with moderate to severe disease that is unresponsive to more conventional systemic therapies (i.e., antibiotics).
III. 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. While 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. The European Dermatology Forum evidence review notes this and suggests that adalimumab be considered for first-line treatment in patients with more severe disease. 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.

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Uveitis and Panuveitis

Initial Evaluation

I. **Adalimumab (Humira)** may be considered medically necessary when the following criteria below are met:
   A. Member is two years of age or older; **AND**
   B. Member is being managed by, or in consultation with, an ophthalmologist or rheumatologist; **AND**
   C. 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.

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.)

Supporting Evidence

I. 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.
II. 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.
III. 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.

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Giant Cell Arteritis

Initial Evaluation

I. **Tocilizumab (Actemra)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **giant cell arteritis** when the following are met:
      1. Presence of at least three of the following:
         i. Age at disease onset of at least 50 years

ii. New onset headache at time of diagnosis
iii. Temporary artery abnormality (tenderness to palpation or decreased pulsation)
iv. Elevated ESR
v. Abnormal artery biopsy; **AND**

2. 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 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 giant cell arteritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. 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 ($p < 0.001$).
II. 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 has not been officially endorsed by the ACR.
III. 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. A large proportion of patients, however, will not have return/relapse of giant cell arteritis after a successful taper of prednisone over one to two years, and in most cases, relapses do not lead to major adverse effects such as vision loss. Glucocorticoids are thus 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.

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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 12 years of age or older; **AND**
   B. Member is being managed by or in consultation with a rheumatologist; **AND**
   C. A diagnosis of **CAPS, including FCAS or MWS**; **AND**
   D. 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. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist; **AND**
   C. Member has a history of three or more episodes of pericarditis; **AND**
   D. 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) noted 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 another 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 (Actemra)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pulmonologist or rheumatologist; **AND**
   C. Tocilizumab (Actemra) will not be used in combination with nintedanib (Ofev) or pirfenidone (Esbriet); **AND**
   D. 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.

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))

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.

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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. Polymyalgia Rheumatica
    A. A phase III placebo-controlled study (n = 40) of etanercept demonstrated mild reduction in disease severity scores, though the response was only analyzed at two weeks. The TNF inhibitor infliximab was also examined in a RCT (n = 51). No statistical difference was observed in relapse between the infliximab and standard of care groups. A phase III study is currently recruiting looking at the IL-6 inhibitors tocilizumab and sarilumab use in this population.

XII. 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 requires 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.

XIII. 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.

XIV. 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.

XV. 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,

XVI. 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).

XVII. 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.

XVIII. 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 month 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.

XIX. 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.

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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) Inhibitor in Chronic Inflammatory Disease Policy	Rheumatoid Arthritis
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)
	Psoriatic Arthritis
	Plaque Psoriasis
	Ankylosing Spondylitis
	Non-radiographic axial spondyloarthritis (nr-axSpA)
	Ulcerative Colitis
	Atopic Dermatitis
Multiple Sclerosis Policy	Multiple Sclerosis
nintedanib (Ofev®); prifenidone (Esbriet®) Policy	Systemic sclerosis-associated interstitial lung disease (SSc-ILD)
Tapinarof (Vtama®)	Plaque Psoriasis

Policy Implementation/Update

Action and Summary of Changes	Date
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 <u>Ulcerative Colitis</u> • Added ustekinumab (Stelara) per FDA indication	11/2019
Criteria updated to new policy format. Specific changes include: <u>Rheumatoid Arthritis</u> • 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 <u>Polyarticular Juvenile Idiopathic Arthritis (PJIA)</u> • 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 <u>Systemic Juvenile Idiopathic Arthritis (SJIA)</u> • 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 <u>Psoriatic Arthritis</u> • 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."	08/2019

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 o Addition of IV corticosteroids as appropriate for this level of severity • Addition of breakdown to Crohn's disease with surgical resection completed or planned o With further addition requiring presence of one additional factor demonstrating medical necessity of biologic treatment Ulcerative Colitis • Added age of 18 years or older • Addition of trial of thiopurine for at least 8 weeks • Added ustekinumab (Stelara) per FDA indication Behcet's Disease • New indication added following approval of Otezla in this setting • Literature supports TNF therapy in oral and ophthalmic manifestations for Bechet'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 Hidradentitis Suppurativa • Updated prescriber language to be consistent with other sections • Added requirement of a trial of antibiotics for moderate disease Uveitis/Panuveitis • Added age of 2 years or older • Improved trial/fail wording to state "ineffective, contraindicated, or not tolerated" o No changes to trial and failure requirements Giant Cell Arteritis (GCA) • 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 Cryopyrin-Associated Periodic Syndromes (CAPS) • 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