Systemic Janus Associated Kinase (JAK) Inhibitors in Chronic Inflammatory Disease
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO246

Description
These agents target the JAK/STAT (janus associated kinase/signal transducer and activator of transcription) pathway that involves proteins, cytokines, and other inflammatory mediators that lead to immune activation and inflammation in chronic inflammatory disease states. The purpose of this policy is to ensure the appropriate use of these agents.

Length of Authorization
- Initial:
  i. Upadacitinib (Rinvoq) 45 mg XR tablet
     - Ulcerative Colitis – two months; two fills/year (one induction treatment per year)
     - Crohn's Disease – three months; three fills/year (one induction treatment per year)
  ii. All other medications: six months
- Renewal:
  i. Upadacitinib (Rinvoq) 45 mg XR tablet: No renewal
  ii. All other medications: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit*
abrocitinib (Cibinqo™)	Atopic Dermatitis (AD)	100 mg tablet	30 tablets/30 days
		200 mg tablet	
baricitinib (Olumiant®)	Rheumatoid Arthritis (RA)	1 mg tablet	30 tablets/30 days
		2 mg tablet	
	Alopecia areata§	2 mg tablet	N/A
		4 mg tablet	N/A
	COVID-19‡	4 mg tablet	N/A
deucravacitinib (Sotyktu™)	Plaque Psoriasis	6 mg tablet	30 tablets/30 days
upadacitinib (Rinvoq™)	Rheumatoid Arthritis (RA) Ankylosing spondylitis (AS) Non-radiographic axial spondyloarthritis (nr-axSpA) Giant Cell Arteritis (GCA)	15 mg XR tablet	30 tablets/30 days
	Atopic Dermatitis (AD)	15 mg XR tablet	30 tablets/30 days
		30 mg XR tablet	
	Ulcerative Colitis (UC) Crohn's Disease (CD)	15 mg XR tablet	30 tablets/30 days
		30 mg XR tablet	
		45 mg XR tablet	28 tablets/28 days
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	1mg/ mL oral solution	Weight-based dosing:

	Psoriatic arthritis (PsA)	(180ml bottle)	• 10 kg -20 kg: 1 bottle/ 30 days • 20 kg – 30 kg: 1 bottle/ 22 days • 30 kg and over: 1 bottle/ 15 days
		15mg XR tablet	Body weight ≥30kg: 30 tablets/30 days**
tofacitinib (Xeljanz®)	Ankylosing spondylitis (AS) Rheumatoid Arthritis (RA) Psoriatic Arthritis (PsA)	5 mg tablet	60 tablets/30 days
		11mg XR tablet	30 tablets/30 days
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	1mg/mL oral solution (240ml bottle)	Weight-based dosing: • 10 kg-20 kg: 1 bottle/30 days • 20 kg-40 kg: 1 bottle/30 days • Body weight ≥40 kg: 1 bottle/24 days
		5 mg tablet	Body weight ≥40 kg: 60 tablets/30 days**
	Ulcerative Colitis (UC)	5 mg tablet	60 tablets/30 days
		10 mg tablet	
		11 mg XR tablet	30 tablets/30 days
		22 mg XR tablet	

**Lower doses may be used in renal and/or hepatic impairment, lymphopenia, neutropenia, anemia, strong CYP3A4 inhibitors (e.g., ketoconazole), strong CYP2C19 inhibitor(s) (e.g., fluconazole)*

§*Treatment for alopecia areata falls in the category of medications that are not covered under the prescription benefit. Drugs used for cosmetic purposes and/or to promote hair growth are excluded from coverage. Please reference the member handbook/certificate of coverage for further information.*

*** Dosing for PJIA is based on body weight. Patients with body weight greater than ≥40kg on the oral solution may be switched to Xeljanz 5 mg tablets or greater than ≥ 30kg may move to Rinvoq XR 15mg tablets.*

‡*Use of baricitinib (Olumiant) in the COVID-19 setting is indicated in hospitalized adults only. Per FDA label dosing is for 14 days or until hospital discharge, whichever occurs first. Review of coverage falls within the medical benefit and is excluded from the pharmacy benefit for this indication.*

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 requirements 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 tumor necrosis factor (TNF) 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 JAK inhibitors with concomitant biologics or with potent immunosuppressants such as azathioprine and cyclosporine are not recommended as there is insufficient data to support 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 this policy.

Rheumatoid Arthritis

I. **Baricitinib (Olumiant), upadacitinib (Rinvoq), or tofacitinib (Xeljanz/Xeljanz XR)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **rheumatoid arthritis** when the following are met:
      1. Treatment with an oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective or not tolerated, or all are contraindicated (e.g., guidelines direct to methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.); **AND**
   C. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], tocilizumab-aazg (Tyenne), and etanercept (Enbrel) 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. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat rheumatoid arthritis or another auto-immune condition (e.g., Humira, Otezla, Remicade, etc.).

Supporting Evidence

I. The agents listed above are approved for adult patients with rheumatoid arthritis (RA) that had an inadequate response or intolerance to TNF inhibitors 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 with highly active RA despite treatment with csDMARDs may receive a bDMARD or JAK inhibitor based on high level of evidence. Biologic DMARDS (TNF-inhibitors, IL-6 inhibitors, etc.) were previously recommended over JAK inhibitors, but newer data comparing JAK inhibitors to adalimumab failed to demonstrate clinically relevant endpoints favoring bDMARDs over JAK inhibitors.

IV. There are currently no head-to-head trials comparing the safety and efficacy of Xeljanz, Rinvoq, or Olumiant in patients with rheumatoid arthritis.

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.
6. Wang F, Sun L, Wang S, et al. Efficacy and Safety of Tofacitinib, Baricitinib, and Upadacitinib for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Mayo Clin Proc*. 2020;95(7):1404-1419.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Initial Evaluation

I. **Tofacitinib (Xeljanz) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **Polyarticular Juvenile Idiopathic Arthritis (PJIA)** when the following are met when the following are 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; **AND**

C. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], tocilizumab-aazg (Tyenne), and etanercept (Enbrel) 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 polyarticular juvenile idiopathic arthritis or another auto-immune condition (e.g., Humira, Orencia, Actemra, Remicade, etc.)

Supporting Evidence

I. The above agent is approved for pediatric patients greater than two years of age with polyarticular juvenile idiopathic arthritis that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
II. Juvenile idiopathic arthritis (JIA) is a grouping of inflammatory disorders that affect children. Polyarticular juvenile idiopathic arthritis (PJIA) is a subset of JIA, which is defined by the presence arthritis in five or more joints during the first six months of illness. Other subsets of JIA include ERA, oligoarthritis (less than five joints affected), systemic juvenile idiopathic arthritis (SJIA; fever, rash, hepatic/splenic/lymphatic involvement), and psoriatic arthritis (psoriasis and dactylitis). While these are distinct disease states, their pathogenesis and presentation are similar so there is significant overlap in effective treatments.
III. The 2019 JIA ACR guidelines for non-systemic polyarthritis (PJIA) 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.

V. Upadacitinib (Rinvoq) was approved in PJIA based on pharmacokinetic data supporting safe plasma exposure in pediatric participants at the predicted dosages thought to be comparable to those observed in adults with RA and PsA. An open-label, Phase I, part 3 clinical trial demonstrated safety and efficacy in 83 patients ages two to 17. Participants not controlled on a biologic DMARD received weight-base dosing upadacitinib (Rinvoq) up to 156 weeks. Upadacitinib (Rinvoq) was well tolerated and led to improvements in disease activity and physical function based on the JIA ACR 30, 50, and 70 responses and the Juvenile Arthritis Disease Activity scores at week 12. The efficacy was generally consistent with responses in patients with rheumatoid arthritis.

VI. Dosing for PJIA is based on body weight. Patients with body weight greater than ≥40kg on the oral solution may be switched to Xeljanz 5 mg tablets. Similarly, those with body weight greater than ≥30kg on the oral solution of Rinvoq may be changed to XR 15mg tablets.

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. Tofacitinib (Xeljanz/Xeljanz XR) [Prescribing Information]. New York, NY; Pfizer Inc., Updated December 2021.
3. Upadactinib (Rinvoq/Rinvoq LQ) [Prescribing information]. North Chicago, IL; AbbVie Inc,. Updated April 2024
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7. Safety and Tolerability of Tofacitinib for Treatment of Polyarticular Course Juvenile Idiopathic Arthritis. 2020 [PROPEL Study] (NCT02592434)
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Psoriatic Arthritis

Initial Evaluation

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

II. **Upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Member is 18 years of age or older; **AND**
      1. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], and secukinumab (Cosentyx) have been ineffective, contraindicated, or not tolerated; **OR**
   C. Member is two to five years of age; **AND**
      1. Treatment with secukinumab (Cosentyx) has been ineffective, contraindicated, or not tolerated; **OR**
   D. Member is six to 17 years of age; **AND**
      1. Treatment with secukinumab (Cosentyx) and ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], have been ineffective, contraindicated, or not tolerated.

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., Humira, Otezla, Olumiant, etc.)

Supporting Evidence

I. Tofacitinib (Xeljanz/Xeljanz XR) and upadacitinib (Rinvoq) are approved for adult patients with psoriatic arthritis (PsA) that had an inadequate response or intolerance to tumor necrosis factor (TNF) inhibitors based on safety and efficacy data from randomized-controlled trials. In April 2024, upadacitinib (Rinvoq) received an age expansion in pediatric patients two years of age and older based on pharmacokinetic data supporting safety and efficacy.
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, prefer 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. 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).
IV. 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). As of January 2022, guidelines have not been updated to place upadacitinib in the PsA treatment algorithm.

References

1. Tofacitinib (Xeljanz/Xeljanz XR) [Prescribing Information]. New York, NY; Pfizer Inc., Updated December 2021.
2. Upadacitinib (Rinvoq) [Prescribing Information]. North Chicago, IL; AbbVie. Updated April 2024.
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Ankylosing Spondylitis

Initial Evaluation

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

Supporting Evidence

I. Tofacitinib (Xeljanz) and upadacitinib (Rinvoq) are approved for adult patients with active ankylosing spondylitis (AS or ax-SpA) that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.

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

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

IV. Diagnosis of SpA is challenging which requires weighing of multiple risk factors and is based on clinical presentation in combination with laboratory and imaging tests and exclusion of other more likely diagnoses. Importantly, diagnosis is not made based on Assessment of SpondyloArthritis international society (ASAS) axSpA classification criteria, which is only used for research purposes. Although inflammatory back pain alone is not sufficient to diagnose SpA, its presence is an important initial step in preselection of patients with a high probability of SpA. Other typical features of SpA include good initial response to NSAIDs, peripheral manifestations,

EMMs, positive family history, elevated lab markers such CRP and ESR, and HLA-B27 positivity. Imaging (plain radiography or X-ray) can detect sacroiliitis of the axial skeleton in patients with radiographic changes (AS). Patients that are not positive for sacroiliitis by plain imaging or X-rays can undergo MRI to detect inflammatory changes of the joints. Patients without abnormalities on imaging (X-ray or MRI) but with other SpA typical features (symptoms, lab markers, etc.) can be diagnosed with nr-axSpA.

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

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

VII. For those patients with inadequate response despite continuous NSAID treatment, the 2019 ACR/SAA/SPARTAN panel recommends the use of TNF inhibitors as the preferred next choice due to experience and familiarity with their long-term safety and toxicity. Guidelines do not recommend any particular TNF inhibitor as the preferred choice. For those patients with continued active disease, the panel conditionally recommends a trial of a different TNF inhibitor over treatment with a non-TNF inhibitor in patients with secondary nonresponse to TNF

inhibitor (those that initially responded and subsequently lost response over time). In patients that never responded to a first trial of a TNF inhibitor (primary nonresponse), trial of a different TNF inhibitor is not recommended and use of subsequent biologics of JAK inhibitors is preferred. Patients presenting with peripheral arthritis symptoms have additional treatment options before escalating to a biologic, which include sulfasalazine and local glucocorticoid (GC) injections. GC injections may also be used in patients with isolated sacroiliitis.

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

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

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

XI. 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.

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Non-radiographic Axial Spondyloarthritis

Initial Evaluation

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

Supporting Evidence

I. Upadacitinib (Rinvoq) is the only JAK inhibitor that is FDA-approved for adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.

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

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

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

the plantar fascia ligament into the calcaneus, and dactylitis (sausage digits) manifests as swollen digits. Lastly, extramusculoskeletal manifestations (EMMs) are possible, which include uveitis/iritis, skin psoriasis, and inflammatory bowel disease (IBD). In patients SpA and comorbid EMMs, comorbidities often guide therapeutic choices.

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

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

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

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

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

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

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

XI. According to the 2022 ASAS-EULAR and 2019 ACR/SAA/SPARTAN guidelines, treatment decisions may differ for patients presenting with EMMs. For example, for those with SpA and comorbid uveitis/iritis, adalimumab, infliximab, golimumab, and certolizumab pegol may be preferred over etanercept as this TNF inhibitor showed contradictory results. Secukinumab was shown to be unsuccessful in patients with non-infectious uveitis while rates of uveitis flares with ixekizumab have not been well-defined. For patients with comorbid inflammatory bowel disease

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

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

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

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Plaque Psoriasis

Initial Evaluation

I. **Deucravacitinib (Sotyktu)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with a dermatologist; **AND**
   B. Not used in combination with other biologics or other non-biologic specialty medications [e.g., apremilast [Otezla], adalimumab (Humira), risankizumab (Skyrizi)] used to treat autoimmune conditions; **AND**
   C. A diagnosis of **moderate-to severe-plaque psoriasis** when the following are met:
      1. Chronic disease (greater than 6 months); **AND**
      2. At least 10% body surface area is involved or involves areas of the face, ears, hands, feet or genitalia; **AND**
      3. 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, etc.); **AND**
      4. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], and secukinumab (Cosentyx) have been ineffective, contraindicated, or not tolerated.

II. Deucravacitinib (Sotyktu) investigational when used for all other conditions, including but not limited to:
   A. Psoriasis in pediatric and adolescent patients
   B. Psoriatic arthritis
   C. Lupus erythematosus
   D. Inflammatory bowel disease

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. Deucravacitinib (Sotyktu) has been evaluated for the treatment of moderate-to-severe plaque psoriasis in adult patients at a dose of 6 mg daily. Guidelines define moderate psoriasis to be 3-10% of the body surface area (BSA) and severe is defined as greater than or equal to 10% BSA involvement. Psoriasis can be considered severe irrespective of BSA when it occurs in certain locations (e.g., hands, feet, face, genital area). Guidelines provide a Grade A recommendation for use of biologics and apremilast (Otezla) for the treatment of moderate-to-severe plaque psoriasis. Guidelines do not point to a specific agent or class when initiating treatment with a biologic or other oral specialty therapy. Flares of psoriasis may be transient and may not require systemic therapy; thus, disease duration of six months is required to determine medical necessity for systemic therapy.

II. Guidelines indicate that the majority of patients are capable of adequately controlling disease solely with topical medications or phototherapy. Phototherapy is recognized as a beneficial therapy for controlled plaque psoriasis and is a cost-effective treatment strategy. Additionally, oral immunomodulatory medications (e.g., methotrexate, cyclosporine, acitretin) are cost-effective therapies with a well-known safety profile for the treatment of plaque psoriasis. For moderate-to-severe disease, where a JAK inhibitor or biologics are warranted, deucravacitinib (Sotyktu) is one of many options. However, it would not be indicated for mild psoriasis given that patients are better managed from a safety perspective on well-established therapies (e.g., topical agents, phototherapy, conventional DMARDS, apremilast [Otezla]). Although deucravacitinib (Sotyktu) has been evaluated and showed to be superior to apremilast (Otezla) in clinical trials for patients with moderate to severe psoriasis, regarding the extent of patients able to achieve outcomes such as PASI75 and PGA0/1, results cannot be readily applied to patients with mild psoriasis. Given the largely unknown safety profile of deucravacitinib (Sotyktu) overall, the risk-to-benefit ratio of using deucravacitinib (Sotyktu) in mild disease is unknown. Alternatively, established therapies should continue to be the mainstay of therapy for these patients.

III. In terms of efficacy, deucravacitinib (Sotyktu) has shown superiority only to apremilast (Otezla) in clinical trials; however, it joins many other efficacious therapies that have well-established safety profiles (e.g., TNF-a inhibitors, IL-17, IL23 therapies). In clinical trials, 50-60% patients on deucravacitinib (Sotyktu) met PASI75. When indirectly comparing, it is not likely superior to the majority of established biologics for psoriasis. Additionally, within the last few years, there has been great improvement in outcomes patients are able to achieve with newer, targeted therapies for psoriasis. Notably, the potential for patients reaching PASI90 and PASI100 within a year of treatment has greatly increased, leading to a rethinking of primary and secondary endpoints evaluated as the standard. For example, 40-60% of patients treated with IL-17 and IL-23 therapies met PASI100 at one year in recent clinical trials. Given established safety profiles, known efficacy, and cost-effectiveness, trial of preferred psoriasis therapies such as biologics as listed in the criteria, are required for trial and failure or intolerance, unless contraindicated.

IV. In subgroup analyses in deucravacitinib (Sotyktu) trials patients with a BMI of 35 kg/m2 or greater may not as readily respond to deucravacitinib (Sotyktu) compared to patients under 35 kg/m2 BMI with otherwise similar characteristics; however, there is no evidence for safety and

efficacy for up dosing beyond 6 mg. There is largely unknown safety profile for this new JAK therapy, and the full extent of the safety profile is likely to be realized from real-world data when duration of use is extended and used in larger patient populations. Until data are available to confirm safety and efficacy of more than 6 mg per day, quantity exceptions will not be allowed.

Investigational or Not Medically Necessary Uses

I. Deucravacitinib (Sotyktu) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Psoriasis in pediatric and adolescent patients
   B. Psoriatic arthritis
   C. Lupus erythematosus
   D. Inflammatory bowel disease

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Crohn's Disease

Initial Evaluation

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

kfce (Yesintek), ustekinumab-stba (Steqeyma)] has been ineffective, contraindicated, or not tolerated.

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. Upadacitinib (Rinvoq) is FDA approved for the treatment of moderate to severe Crohn's Disease (CD) based on safety and efficacy data from randomized-controlled trials. Certolizumab pegol (Cimzia), ustekinumab (Stelara), risankizumab (Skyrizi) and upadacitinib (Rinvoq) 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 the 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 the presence of active inflammation, and therefore should not be the sole guide for therapy. Objective evaluation by endoscopic imaging should be undertaken to avoid errors of under or overtreatment.
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 the 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), risankizumab (Skyrizi), and upadacitinib (Rinvoq) 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.

High-risk/severe CD

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

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.

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Ulcerative Colitis

Initial Evaluation

I. **Tofacitinib (Xeljanz/Xeljanz XR) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   B. Diagnosis of **moderate to severe ulcerative colitis; AND**
   C. Provider attestation or clinical documentation of at least one of the following:
      1. Treatment with systemic corticosteroids (e.g., prednisone, budesonide) has been ineffective, contraindicated, or not tolerated; **OR**
      2. Treatment with an immunomodulator (e.g., azathioprine, 6-mercaptopurine) has been ineffective, contraindicated, or not tolerated; **AND**
   D. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)] and ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)] has been ineffective, contraindicated, or not tolerated.

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. Tofacitinib (Xeljanz/Xeljanz XR) and upadacitinib (Rinvoq) are FDA approved in the treatment of moderate to severe ulcerative colitis (UC) in adult patients over eighteen years of age that had an inadequate response or intolerance to one or more TNF inhibitors based on safety and efficacy data from randomized-controlled trials. 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), ozanimod (Zeposia), upadacitinib (Rinvoq), mirikizumab (Omvoh), etrasimod (Velsipity), infliximab-dyyb (Zymfentra), and risankizumab (Skyrizi), have not been evaluated in head-to-head trials to compare the efficacy and safety between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), upadacitinib (Rinvoq), mirikizumab (Omvoh), etrasimod (Velsipity), infliximab-dyyb (Zymfentra), and risankizumab (Skyrizi) is incremental or better when evaluated against placebo. 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. The 2019 American College of Gastroenterology (ACG) clinical guideline on the management of ulcerative colitis in adults recommend oral systemic corticosteroids for induction of remission in moderate to severe disease (strong recommendation, moderate quality of evidence). TNF inhibitors (adalimumab, golimumab, and infliximab), vedolizumab (Entyvio), and tofacitinib (Xeljanz) are also recommended for induction of remission (strong recommendation, moderate quality of evidence). For maintenance of remission, thiopurines are recommended if remission was achieved after corticosteroid induction (conditional recommendation, low quality of evidence). The guidelines note a systematic review of 1,632 patients with ulcerative colitis demonstrated that azathioprine and mercaptopurine had a 76% mean efficacy in maintaining remission. If remission was achieved with anti-TNF therapy, vedolizumab (Entyvio), or tofacitinib (Xeljanz), clinical guidelines support continuing with the same agent to maintain remission (strong recommendation, moderate quality of evidence). The 2020 American Gastroenterology Association (AGA) guidelines make similar recommendations. Additionally, AGA recommends early use of biologic agents, rather than gradual step up after failure of 5-ASA in moderate to severe disease at high risk for colectomy. However, the overall quality of evidence supporting this recommendation was rated as very low. Guidelines also note that for patients with less severe disease, 5-ASA therapy may still be a reasonable choice of therapy to start with. For maintenance of remission, AGA makes no recommendation in favor of, or against, using biologic monotherapy, rather than thiopurine monotherapy due to absence of evidence. As of May 2022, the guidelines have not been updated to include upadacitinib (Rinvoq).

IV. 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.

V. 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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Atopic Dermatitis

Initial Evaluation

I. **Upadacitinib (Rinvoq) or abrocitinib (Cibinqo)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a dermatologist or an allergist; **AND**
   B. A diagnosis of **moderate to severe atopic dermatitis** when the following are met:
      1. Body surface area (BSA) involvement of at least 10%; **OR**
         i. Involves areas of the face, ears, hands, feet, or genitalia; **AND**
      2. Treatment with at least two of the following groups has been ineffective or not tolerated, or 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., tacrolimus ointment, pimecrolimus cream)
iii. Group 3: topical PDE-4 inhibitor (crisaborole [Eucrisa]); **AND**

C. Treatment with dupilumab (Dupixent) 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. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat atopic dermatitis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, BSA involvement, pruritis symptoms)

Supporting Evidence

I. Atopic dermatitis (AD), also known as atopic eczema, is an inflammatory skin condition most frequently occurring in pediatric patients. It manifests with pruritis, dry skin, crusting, and serous oozing causing chronic scratching which leads to blister formation, skin thickening (lichenification), fissuring, or lesions. This condition is associated with elevated serum IgE and it is often a comorbid condition with asthma and allergic conditions.
II. Treatments for mild-to-moderate AD include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), phototherapy, and/or crisaborole (Eucrisa) – a PDE4 inhibitor. Symptomatic treatments include oral and topical antihistamines and sleep aids for nighttime pruritus. Treatment choice between these products is dependent on severity, location, and other patient specific factors (e.g., allergies, age). According to AAD guidelines, TCIs may be preferable to TCS in patients with recalcitrance to steroids, sensitive areas involved, steroid-induced atrophy, and long-term uninterrupted topical steroid use.
III. Treatment for moderate to severe disease not amenable to topicals includes systemic immunosuppressants (e.g., corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), JAK inhibitors (e.g., abrocitinib, upadacitinib), and dupilumab (Dupixent), a biologic IgG4 that is FDA-approved for pediatrics and adults as a biologic option for moderate-to-severe AD. Currently, there are no head to head trials evaluating safety and/or efficacy differences or superiority between biologic therapies in atopic dermatitis. Dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis

and is approved down to six years of age. Upadacitinib (Rinvoq) and abrocitinib (Cibinqo) have been evaluated and are FDA approved in patients down to 12 years of age.

IV. There may be patient specific scenarios in which the use of additional topical agents following failure of one class of topical agents would be impractical. Insight from dermatology specialists indicate that patients who have at least 15% BSA involvement, or involvement in sensitive areas (e.g., eyelids, axilla, genitals, gluteal cleft), and have severe disease are potential candidates for systemic biologic therapy. Severe disease, as defined by NICE guidelines, include widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation), and severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep; severe disease can also be classified as physician's global assessment (PGA) score of 4.0. Additionally, administration of topical agents may become impractical for patients with a high disease burden (BSA ≥ 20%), considering twice daily administration is necessary for non-steroid topical agents for optimal efficacy.

V. Upadacitinib (Rinvoq) is FDA approved in patients with moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable. Similarly, abrocitinib (Cibinqo) is FDA approved in patients with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Due to safety concerns, use of other systemic drugs is recommended prior to use of upadacitinib (Rinvoq) and abrocitinib (Cibinqo).

VI. There is lack of head-to-head clinical trial data for the AD FDA-approved therapies, and superior safety and efficacy of any product cannot be confidently concluded. Thus, it is reasonable that pending no contraindication to therapy, preferred therapies be based on cost-effectiveness.

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Giant Cell Arteritis

Initial Evaluation

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

Supporting Evidence

I. Giant cell arteritis (GCA) is an inflammatory vascular condition that is most frequently occurring in adult patients 50 years of age or older. It manifests with fever, fatigue, headache, transient or permanent vision loss, and large vessels involved like the aorta, and major vessels in upper extremities. Large vessel involvement includes dissections, aneurysm, tenderness to palpation, or asymmetric blood pressure. This condition is associated with elevated serum ESR and CRP levels and it is often closely related to polymyalgia rhematic disease.
II. In 2022 ACR/EULAR came out with updated classification criteria for giant cell arteritis. These criteria have demonstrated a sensitivity of 87% and a specificity of 94.8%. Current ACR guidelines are from 2021, therefore this new classification criteria are not included in the most current guidelines.
III. The 2021 American College of Rheumatology guidelines for GCA recommends starting high dose daily glucocorticoids, or tocilizumab with glucocorticoids or tocilizumab alone in newly diagnosed GCA. Patients with active extracranial large vessel involvement OR disease relapse with symptoms of cranial ischemia may start tocilizumab and glucocorticoids or start methotrexate with glucocorticoids if tocilizumab is not an option due to cost or tolerability. Guidelines have not been updated to include upadacitinib (Rinvoq).
IV. Upadacitinib (Rinvoq) is FDA approved for adults with GCA based off results of a Phase 3 RCT (SELECT-GCA). In this trial 428 patients were randomized to oral upadacitinib (Rinvoq) plus a prednisone taper or placebo plus a prednisone taper. The primary outcome of glucocorticoid-free remission was statistically significant, with 46% in the upadacitinib (Rinvoq)15 mg group compared to 29% in the placebo group (17% treatment effect, $p = 0.002$). The safety profile of upadacitinib (Rinvoq) is similar to what is seen with other indications.
V. 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 was 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 ($p < 0.001$).
VI. Although upadacitinib is an FDA-approved medication for GCA, tocilizumab (Actemra) has equal or greater safety and efficacy data to support its use in this condition. There are also no current head-to-head trials comparing upadacitinib (Rinvoq) to tocilizumab (Actemra) in GCA. Guidelines have consensus regarding the use of tocilizumab (Actemra); however, there is no consensus on the use of upadacitinib (Rinvoq) due to the newer approval.
VII. Standard dosing of upadacitinib (Rinvoq) for GCA is 15 mg once daily.

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Investigational or Not Medically Necessary Uses

I. Combination use with topical and systemic JAK inhibitors
   A. The safety profile of systemic JAK inhibitors is continuing to develop; however, the FDA has issued cardiovascular and malignancy warnings. The true safety profile of ruxolitinib is unknown at this time, given the short trial duration and relatively small trial population. Utilizing a systemic JAK therapy in addition to topical JAK therapy (ruxolitinib) has unknown, and potentially additive, risks. Until further data are available to establish a safety profile with this combination, dual use will be disallowed.

II. COVID-19 or associated symptoms or complications
   A. The role of JAK-inhibitors in the treatment of COVID-19 is evolving and varies among available guidelines. Long-term data is not available and continuing therapy beyond hospitalization has not been evaluated for safety and efficacy.

III. Various dermatologic conditions (including, but not limited to plaque psoriasis, guttate psoriasis, vitiligo, dermatomyositis, lichen planus)
   A. Case reports suggest that the use of TNF inhibitors may induce flares when used for guttate psoriasis. 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, JAK inhibitors, or targeted DMARDs in this setting at this time.
   B. A systematic review by Ciechanowich et al. evaluated the use of JAK inhibitors in psoriasis, atopic dermatitis, and vitiligo. Seventeen studies (11 randomized controlled trials, 4 case reports, 1 retrospective case series, and 1 open-label clinical trial) were included in the review and concluded that there is limited data to suggest the safety and efficacy of JAK inhibitors in various dermatologic diseases outside of FDA-approved indications. As of November 2022, deucravacitinib (Sotyktu) is the only JAK inhibitor FDA-approved to treat plaque psoriasis; upadacitinib (Rinvoq) and abrocitinib (Cibinqo) are FDA-approved to treat atopic dermatitis.

IV. Alopecia Areata/Alopecia Totalis/Alopecia Universalis
   A. Baricitinib (Olumiant) has FDA approval for alopecia areata; therapies for alopecia are in a category of medications that are not covered under the prescription benefit. Drugs used

for cosmetic purposes and/or to promote hair growth are excluded from coverage. Of note, not all JAK inhibitors have been evaluated or are FDA-approved for this condition.

V. Atopic Dermatitis – Olumiant (baricitinib)
   A. Two phase III, double-blind, multicenter monotherapy trials BREEZE-AD1 and BREEZE-AD2 studies concluded baricitinib 2mg, 4mg reached its primary endpoint of Validated Investigator's Global Assessment at week 16 compared to placebo. The manufacturer reports a statistical improvement in Investigator's Global Assessment (IGA) scores at week 16 compared to placebo, baricitinib improved clinical signs and symptoms in patients with moderate-to-severe AD within 16 weeks of treatment and induced rapid reduction of itch. The safety profile remained consistent with prior findings from baricitinib clinical development in AD, with no new safety concerns. The drug remains in clinical development and is considered experimental and investigational at this time. Three clinical trials are currently ongoing which may provide further confirmation of safety and efficacy.

VI. 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.

VII. Lupus Nephritis, Systemic Lupus Erythematosus (SLE), and Cutaneous Lupus Erythematosus (CLE)
   A. In a 24-week phase II RCT evaluated baricitinib in adults with highly active SLE exhibiting skin and joint symptoms despite the standard treatment, 314 patients were randomly assigned to receive placebo, baricitinib 2 mg, or baricitinib 4 mg. At week 24, baricitinib 4 mg dose (p=0.0414), but not the 2 mg dose, improved the signs and symptoms of active SLE. The short follow-up/study design limits the findings from this study.
   B. Lilly and Incyte have decided to end lupus development for Olumiant (baricitinib) after receiving topline efficacy data from two Phase III studies (SLE-BRAVE 1 and SLE-BRAVE 2) in adults with active lupus. While Olumiant (baricitinib) reached the primary endpoint in one trial (SLE-BRAVE 1), follow up trial (SLE-BRAVE 2) failed to meet the primary endpoint and neither trial achieved key secondary endpoints.

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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
Chronic Inflammatory Disease Policy	Rheumatoid Arthritis
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)
	Enthesitis-Related Arthritis (ERA)
	Systemic Juvenile Idiopathic Arthritis (SJIA)
	Psoriatic Arthritis
	Ankylosing Spondylitis
	Non-radiographic Axial Spondyloarthritis
	Plaque Psoriasis
	Crohn's Disease
	Ulcerative Colitis
	Behcet's Disease (i.e., Behcet Syndrome)
	Hidradenitis Suppurativa
	Uveitis and Panuveitis
	Giant Cell Arteritis
	Cryopyrin-Associated Periodic Syndromes (CAPS)
	Recurrent Pericarditis
	Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)
	Polymyalgia Rheumatica
ruxolitinib (Jakafi, Opzelura) Policy	Intermediate or high-risk myelofibrosis
	Polycythemia vera
	Graft-Versus-Host Disease
	Atopic dermatitis
fedratinib (Inrebic) Policy	Myelofibrosis
dupilumab (Dupixent) Policy	Atopic dermatitis
tralokinumab (Adbry) Policy	Atopic dermatitis
tapinarof (Vtama) Policy	Plaque Psoriasis
nemolizumab (Nemluvio) Policy	Atopic Dermatitis
lebrikizumab (Ebglyss) Policy	Atopic Dermatitis
spesolimab SC (Spevigo) Policy	Generalized pustular psoriasis (GPP)

Policy Implementation/Update

Action and Summary of Changes	Date
Live 07/01/2025: Addition of select ustekinumab biosimilars (Selarsdi, Steqeyma, and Yesintek) to preferred. Added criteria for Rinvoq for treatment of GCA.	06/2025
Removed age limitations throughout policy	02/2025
Change to Ankylosing Spondylitis (AS) and Non-radiographic Spondyloarthritis (nr-axSpA) criteria to remove requirements for disease manifestation as axial or peripheral arthritis, change to definition of high disease activity, change to supportive evidence sections. Updated related policies.	11/2024
Update on Rinvoq for age expansion in psoriatic arthritis for those two and older, as well as an approval in juvenile idiopathic arthritis (PJIA). Include tocilizumab-aazg (Tyenne) as a required preferred product for applicable indications.	7/2024
Change to ulcerative colitis criteria to require trial of at least one corticosteroid or immunomodulator; change to Crohn's disease criteria to require trial of at least one corticosteroid or immunomodulator and change to define high-risk Crohn's disease and remove severe Chron's disease	02/2024

Live **TBD**: removal of Skyrizi as a preferred product. Live 02/01/2024: addition of select biosimilars (Hadlima and adalimumab-adaz) as preferred products, removal of brand Humira as a preferred product.	01/2024
Updated Cibinqo age requirements. Update to supporting evidence.	04/2023
Live 06/2023: Added criteria to include new indication for Rinvoq in the setting of Crohn's disease. Updated quantity limit table to include new indication of Crohn's disease for Rinvoq. Updated initial authorization for Rinvoq XR 45mg tablets to two months for Ulcerative Colitis and three months for Crohn's disease, added fill limit of three per year for CD. Updated supporting evidence section and references for Crohn's disease.	03/2023
Review conducted. Update to supporting evidence.	02/2023
Added criteria to include new indication for Rinvoq in the setting at non-radiographic spondyloarthritis. Updated supporting evidence and references for AS and nr-axSpA sections. Updated wording of renewal criteria regarding combination biologic use to reflect specific disease state referenced. Updated E/I supporting evidence for use of JAK inhibitors in dermatologic conditions. Updated related policies section.	11/2022
Addition of new molecular entity, Sotyktu in plaque psoriasis	08/2022
Added new indication for Rinvoq in the setting of active ankylosing spondylitis, updated supportive evidence, and reference section. Added new indication of alopecia areata for baricitinib (Olumiant®) noting this is an excluded indication.	06/2022
Added Rinvoq's new indication of Ulcerative Colitis, updated supportive evidence section, updated formatting; added supportive evidence to Atopic Dermatitis section; added baricitinib (Olumiant)'s new COVID-19 indication and tablet strength in the QL table, removed AS from E/I section given Rinvoq's new FDA approval in AS.	05/2022
Added Cibinqo for the setting of Atopic Dermatitis, built out the Atopic Dermatitis criteria section in the policy for Cibinqo and Rinvoq with new FDA approvals. Updated PJIA supporting evidence and references to further clarify guidelines and treatment algorithm and align with Chronic Inflammatory Disease policy.	03/2022
Added new line indication for Rinvoq in setting of PsA. Updated PA policy to include FDA approval for Xeljanz in AS. Updated supporting evidence sections to include new FDA label requirements limiting use of all oral JAK inhibitors to certain patients who have not responded to or cannot tolerate one or more TNF blockers. Experimental and investigational section updated to include warning on combination of topical and oral JAK inhibitors and alopecia areata. Added new Rinvoq 30mg tablet availability for atopic dermatitis.	02/2022
Created the Systemic Janus Associated Kinase (JAK) Inhibitor in Chronic Inflammatory Diseases policy. Added Related Policies section.	12/2021
Previous policy changes (relevant from Chronic Inflammatory Policy)	
Updated criteria for ulcerative to modify 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 PA policy to include FDA approvals for Xeljanz for PJIA. Updated supporting evidence section with clinical trial data	11/2020
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).	08/2020
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	08/2019

• 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>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." <u>Ulcerative Colitis</u> • Added age of 18 years or older • Addition of trial of thiopurine for at least 8 weeks	
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
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