# 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: up to two months; maximum two fills per 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)<br>Psoriatic arthritis (PsA)<br>Ankylosing spondylitis (AS)<br>Non-radiographic axial spondyloarthritis (nr-axSpA) | 15 mg XR tablet | 30 tablets/30 days |
| | Atopic Dermatitis (AD) | 15 mg XR tablet | |

| | | | |
|---|---|---|---|
| | | 30 mg XR tablet | 30 tablets/30 days |
| | Ulcerative Colitis (UC) | 15 mg XR tablet | 30 tablets/30 days |
| | | 30 mg XR tablet | |
| | | 45 mg XR tablet | 28 tablets/28 days |
| tofacitinib (Xeljanz®) | Ankylosing spondylitis (AS)<br>Rheumatoid Arthritis (RA)<br>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<br>(240ml bottle) | Weight-based dosing:<br>• 10 kg-20 kg: 1 bottle/30 days<br>• 20 kg-40 kg: 1 bottle/30 days<br>• Body weight ≥40 kg: 1 bottle/24 days |
| | | 5 mg tablet | Body weight ≥40 kg:<br>60 tablets/30 days** |
| | Ulcerative Colitis (UC) | 5 mg tablet | 60 tablets/30 days |
| | | 10mg tablet | |
| | | 11mg XR tablet | 30 tablets/30 days |
| | | 22mg 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.*

‡*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 is 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 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **rheumatoid arthritis** when the following are met:
      1. Treatment with an oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective or not tolerated, or all are contraindicated (e.g., guidelines direct to methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.); **AND**
   D. Treatment with adalimumab (Humira) 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)** may be considered medically necessary when the following criteria below are met:
   A. Member is 2 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **Polyarticular Juvenile Idiopathic Arthritis (PJIA)** when the following 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**
   D. Treatment with adalimumab (Humira) 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. 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.

## 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. Ringold S, Angeles-han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care Res (Hoboken). 2019.
4. UpToDate, Inc. Polyarticular juvenile idiopathic arthritis: treatment. UpToDate [database online]. Waltham, MA. Last updated October 19, 2020. Available at: http://www.uptodate.com/home/index.html. Last accessed November 22 ,2021.

5. Brunner H, Ting T, el al. Tofacitinib in treatment of Polyarticular-course Juvenile idiopathic Arthritis: Results of a Phase 3 Randomized Double-blind Placebo withdrawal Study. ACR 2019. Abstract number: L22
6. Safety and Tolerability of Tofacitinib for Treatment of Polyarticular Course Juvenile Idiopathic Arthritis. 2020 [PROPEL Study] (NCT02592434)

## Psoriatic Arthritis

### 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 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist or dermatologist; **AND**
   C. A diagnosis of active **psoriatic arthritis** when the following are met:
      1. Treatment with non-biologic, non-specialty oral small molecules (OSMs) such as methotrexate, leflunomide, sulfasalazine, or cyclosporine has been ineffective, contraindicated, or not tolerated; **OR**
      2. Presence of active, severe disease as indicated by provider assessment and the presence of at least one of the following:
         i. Erosive disease
         ii. Elevated CRP or ESR
         iii. Long-term damage interfering with function (e.g., joint deformities, vision loss)
         *iv.* Major impairment of quality of life due to high disease activity at many sites (including dactylitis, enthesitis) or functionally limiting arthritis at a few sites; **AND**
   D. Treatment with adalimumab (Humira), etanercept (Enbrel), risankizumab (Skyrizi), 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 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.

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

III. 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 2022.
3. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheumatol*. 2019;71(1):5-32.

4. Kingsley GH, Scott DL. Assessing the effectiveness of synthetic and biologic disease-modifying antirheumatic drugs in psoriatic arthritis - a systematic review. Psoriasis (Auckl). 2015;5:71-81.
5. UpToDate, Inc. Treatment of psoriatic arthritis. UpToDate [database online]. Waltham, MA. Last updated November 20, 2020. Available at: http://www.uptodate.com/home/index.html.

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

### Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat ankylosing spondylitis or another auto-immune condition (e.g., 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. The 2019 ACR/SAA/SPARTAN guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% responding). Recommendations against the use of non-biologic DMARDs are made for patients with active ankylosing spondylitis despite NSAID treatment. Some benefit has been seen in patients with peripheral arthritis, thus treatment with sulfasalazine or methotrexate may be considered in patients with predominantly peripheral disease; however, evidence is based on older RCTs with very low quality of evidence. For those patients with inadequate response despite continuous NSAID treatment, the ACR strongly recommends use of TNF inhibitors over no treatment with TNF inhibitors. Moreover, the panel conditionally recommends treatment with secukinumab or ixekizumab over sulfasalazine, methotrexate, or tofacitinib. In patients with primary nonresponse, defined as absence of improvement after 3- 6 months of treatment initiation, secukinumab or ixekizumab is conditionally recommended over switching to a different TNF inhibitor. In patients with secondary nonresponse to TNF inhibitors, the guidelines conditionally recommend treatment with a different TNF inhibitor over treatment with a non-TNF inhibitor biologic. The guidelines have not been updated with regard to place in therapy for upadacitinib as of November 2022.

III. The 2022 ASAS/EULAR guidelines for the treatment of axial spondyloarthritis (axSpA) reference the use of JAK inhibitors in the treatment algorithm. The term axial spondyloarthritis (axSpA), encompasses both active ankylosing spondylitis (or radiographic AS) and nr-axSpA as one entity part of the same chronic inflammatory musculoskeletal spectrum with similar clinical presentations, comorbidities, disease burden, and treatment response. ASAS/EULAR recommends patients try and fail at least 2 NSAIDs over 4 weeks as first line therapy and treat local musculoskeletal inflammation with glucocorticoid injection; sulfasalazine may be considered in patients with peripheral symptoms, however use of conventional non-biologic DMARDS (e.g. sulfasalazine, leflunomide, methotrexate, etc.) is not recommended in axial disease. In contrast to ACR/SAA/SPARTAN, ASAS/EULAR guidelines highly recommend treatment with a TNF inhibitor, IL-17 inhibitor, or JAK inhibitor for patients with high disease activity, defined by a BASDAI of at least 4 or an ASDAS of at least 2.1, despite conventional treatment with NSAIDS. Starting with a TNF inhibitor or IL-17 inhibitor is preferred clinically, given long term data for use of JAK inhibitors in axSpA is still missing. There is no specific treatment algorithm after primary non-response to biologic (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor therapy. In absence of data showing superiority in the treatment sequence, switching to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or a JAK inhibitor may be considered.

IV. Although specific JAK inhibitors were not referenced in the ASAS/EULAR guideline, precautions for cardiovascular risk, malignancy, and thromboembolic events should be considered in patients starting JAK inhibitors. It is unclear whether the increased risk of cardiovascular events and malignancies is specific to a diagnosis of RA, reflective of a JAK inhibitor class effect, or specific to tofacitinib. Until more data become available, ASAS/EULAR advises against starting JAK inhibitors in specific populations: patients above 50 years of age with one or more cardiovascular risk factor and patients older than 65 years of age.

### References

1. Tofacitinib (Xeljanz/Xeljanz XR) [Prescribing Information]. New York, NY; Pfizer Inc., Updated January 2022.
2. Upadacitinib (Rinvoq) [Prescribing Information]. North Chicago, IL; AbbVie. Updated November 2022.
3. Ward, M.M., Deodhar, A., Gensler, L.S, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol*, 71: 1599-1613.
4. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis*. Published online October 21, 2022:ard-2022-223296.
5. UpToDate, Inc. Clinical manifestations of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults. UpToDate [database online]. Waltham, MA. Last updated November 2, 2022. Available at: http://www.uptodate.com/home/index.html.
6. UpToDate, Inc. Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondloarthritis) in adults. UpToDate [database online]. Waltham, MA. Last updated August 24, 2022. Available at: http://www.uptodate.com/home/index.html.
7. UpToDate, Inc. Treatment of peripheral spondyloarthritis. UpToDate [database online]. Waltham, MA. Last updated March 17, 2022. Available at: http://www.uptodate.com/home/index.html.

## Non-radiographic Axial Spondyolarthritis

### Initial Evaluation

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

D. Disease manifested as peripheral arthritis; **AND**
E. Treatment with adalimumab (Humira), etanercept (Enbrel), and secukinumab (Cosentyx) have been ineffective, contraindicated, or not tolerated.

## Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat 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, and secukinumab are the only FDA approved agent for adults with nr-axSpA. 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. Per 2019 ACR/SAA/SPARTAN guidelines for AS and nr-axSpA, 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. As of November 2022, guidelines have not been updated with regard to place in therapy for upadacitinib for nr-axSpA.

IV. The 2022 ASAS/EULAR guidelines for the treatment of axial spondyloarthritis (axSpA) reference the use of JAK inhibitors in the treatment algorithm. The term axial spondyloarthritis (axSpA), encompasses both active ankylosing spondylitis (or radiographic AS) and nr-axSpA as one entity part of the same chronic inflammatory musculoskeletal spectrum with similar clinical presentations, comorbidities, disease burden, and treatment response. ASAS/EULAR recommends patients try and fail at least 2 NSAIDs over 4 weeks as first line therapy and treat local musculoskeletal inflammation with glucocorticoid injection; sulfasalazine may be considered in patients with peripheral symptoms, however use of conventional non-biologic DMARDS (e.g. sulfasalazine, leflunomide, methotrexate, etc.) is not recommended in axial disease. In contrast to ACR/SAA/SPARTAN, ASAS/EULAR guidelines highly recommend treatment with a TNF inhibitor, IL-17 inhibitor, or JAK inhibitor for patients with high disease activity, defined by a BASDAI of at least 4 or an ASDAS of at least 2.1, despite conventional treatment with NSAIDS. Starting with a TNF inhibitor or IL-17 inhibitor is preferred clinically, given long term data for use of JAK inhibitors in axSpA is still missing. There is no specific treatment algorithm after primary non-response to biologic (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor therapy. In absence of data showing superiority in the treatment sequence, switching to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or a JAK inhibitor may be considered.

V. Although specific JAK inhibitors were not referenced in the ASAS/EULAR guideline, precautions for cardiovascular risk, malignancy, and thromboembolic events should be considered in patients starting JAK inhibitors. It is unclear whether the increased risk of cardiovascular events and malignancies is specific to a diagnosis of RA, reflective of a JAK inhibitor class effect, or specific to tofacitinib. Until more data become available, ASAS/EULAR advises against starting JAK inhibitors in specific populations: patients above 50 years of age with one or more cardiovascular risk factor and patients older than 65 years of age.

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## Plaque Psoriasis

### Initial Evaluation

I. **Deucravacitinib (Sotyktu)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with a dermatologist; **AND**
   C. 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**
   D. 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**
         iii. Treatment with adalimumab (Humira), etanercept (Enbrel), secukinumab (Cosentyx), AND Risankizumab (Skyrizi) 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

V. 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.
VI. 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.

VII. In terms of efficacy, deucravacitinib (Sotyktu) has showed 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 to reach 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.

VIII. 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

## References

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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 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   C. A diagnosis of **moderate to severe ulcerative colitis** when the following are met:
      1. Previous treatment with at least one systemic corticosteroid (e.g., budesonide, prednisone, hydrocortisone, methylprednisolone, etc.) has been ineffective to induce remission, is contraindicated, or is not tolerated; **AND**
      2. If systemic corticosteroids were used to induce remission, previous treatment with at least one thiopurine (azathioprine or 6-mercaptopurine) over an eight-week period to maintain remission has been ineffective, contraindicated, or not tolerated; **AND**
   D. Treatment with adalimumab (Humira) has been ineffective, contraindicated, or not tolerated.

### Renewal Evaluation

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

### Supporting Evidence

I. 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. Tofacitinib (Xeljanz), Adalimumab (Humira), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), and upadacitinib (Rinvoq) have not been evaluated in head-to-head trials to

compare the efficacy and safety between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), and golimumab (Simponi) is incremental or better when evaluated against placebo. There is moderate certainty that ozanimod (Zeposia) provides promising but inconclusive net health benefit compared to placebo in patients with moderate to severe UC due to evidence being available from only one phase 3 trial and less established safety data compared to other UC treatment options.

III. The 2019 American College of Gastroenterology (ACG) clinical guideline on the management of ulcerative colitis in adults recommend oral systemic corticosteroids for induction of remission in moderate to severe disease (strong recommendation, moderate quality of evidence). TNF inhibitors (adalimumab, golimumab, and infliximab), vedolizumab (Entyvio), and tofacitinib (Xeljanz) are also recommended for induction of remission (strong recommendation, moderate quality of evidence). For maintenance of remission, thiopurines are recommended if remission was achieved after corticosteroid induction (conditional recommendation, low quality of evidence). The guidelines note a systematic review of 1,632 patients with ulcerative colitis demonstrated that azathioprine and mercaptopurine had a 76% mean efficacy in maintaining remission. If remission was achieved with anti-TNF therapy, vedolizumab (Entyvio), or tofacitinib (Xeljanz), clinical guidelines support continuing with the same agent to maintain remission (strong recommendation, moderate quality of evidence). The 2020 American Gastroenterology Association (AGA) guidelines make similar recommendations. Additionally, AGA recommends early use of biologic agents, rather than gradual step up after failure of 5-ASA in moderate to severe disease at high risk for colectomy. However, overall quality of evidence supporting this recommendation was rated as very low. Guidelines also note that for patients with less severe disease, 5-ASA therapy may still be a reasonable choice of therapy to start with. For maintenance of remission, AGA makes no recommendation in favor of, or against, using biologic monotherapy, rather than thiopurine monotherapy due to absence of evidence. 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

III. **Upadacitinib (Rinvoq) or abrocitinib (Cibinqo)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **OR**
      1. Member is 12 years of age or older and request is for upadacitinib (Rinvoq); **AND**
   B. Medication is prescribed by, or in consultation with, a dermatologist or an allergist; **AND**
   C. 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 <u>two</u> of the following groups has been ineffective or not tolerated, or <u>all</u> 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**

D. Treatment with dupilumab (Dupixent) has been ineffective, contraindicated, or not tolerated.

### Renewal Evaluation

V. 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**

VI. 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**

VII. 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**

VIII. 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)

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) has been evaluated and is FDA approved in patients down to 12 years of age. Abrocitinib (Cibinqo) is FDA approved in adult patients only.

IV. 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. Due to safety concerns, use of other systemic drugs is recommended prior to use of upadacitinib (Rinvoq).

V. 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.

### References

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## Investigational or Not Medically Necessary Uses

II. 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.

III. 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.
IV. 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.
V. 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.
VI. 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.
VII. 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.

VIII. 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 limit 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) |
| 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) | Plaque Psoriasis |

## Policy Implementation/Update

| Action and Summary of Changes | Date |
|---|---|
| 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:<br><u>Rheumatoid Arthritis</u><br>• Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement<br>• Removed requirements for diagnosis due to varying methods to diagnose and limited value of this question from health plan standpoint<br>• Clarified use of oral DMARD requirement may be bypassed if all of them are contraindicated<br>• Added newly approved upadacitinib (Rinvoq) as a non-preferred alternative<br><u>Polyarticular Juvenile Idiopathic Arthritis (PJIA)</u><br>• Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement<br>• Added route to approval of Actemra as Actemra was previously in a separate policy<br><u>Psoriatic Arthritis</u><br>• Added requirement of the presence of active severe disease and provided specific indicators of severe disease<br>• 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."<br><u>Ulcerative Colitis</u><br>• Added age of 18 years or older<br>• Addition of trial of thiopurine for at least 8 weeks | 08/2019 |
| 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:<br>1. 18 years of age requirement has been removed for Stelara as it has now been FDA approved for pediatric plaque psoriasis.<br>2. New FDA approved indication of psoriatic arthritis has been added for Xeljanz/Xeljanz XR and Taltz<br>3. The question regarding dual therapy has been refined to encompass the language of biologics and other non-biologics (e.g. Otezla and Xeljanz).<br>4. The question regarding DMARDs has been refined to only include agents that are administered non-biologic, non-specialty and that are administered orally.<br>5. For the indication of plaque psoriasis, the question addressing the trial of UVB has been combined with the trial of DMARDs. | 01/2018 |