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Subject: Upadacitinib Tablets (Rinvoq®) and Oral Solution (Rinvoq LQ®)

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DESCRIPTION:

Upadacitinib (Rinvoq) is an oral Janus kinase (JAK) inhibitor initially approved by the US Food and Drug Administration (FDA) in August 2019 for “the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate.” Many mediators in autoimmune inflammation (e.g., interleukins 2, 6, 12, 15, and 23; interferons; and granulocyte-macrophage colony-stimulating factor [GM-CSF]) signal through the JAK family (JAK1, JAK2, JAK3, and tyrosine kinase 2 [Tyk2]). Upadacitinib was the third JAK inhibitor to be approved by the FDA for the treatment of RA; the first being tofacitinib (Xeljanz) in November 2012 and the second being baricitinib (Olumiant) in May 2018. Tofacitinib has the greatest affinity for JAK3, but it is generally considered a pan-JAK inhibitor (i.e., inhibitory activity at all, but JAK3>JAK1>>JAK2>>TYK2). Baricitinib inhibits JAK1 and JAK2, and to a much lesser extent TYK2. It is considered a JAK3 sparing agent with a 100-fold selectivity for JAK1 and JAK2. Upadacitinib is a selective JAK1 inhibitor, with 74- and 58 -fold selectivity for JAK1 over JAK2 and JAK3, respectively. This is due to its ability to bind JAK1 at two separate sites. *In vitro* research suggests that JAK1 inhibition might be largely responsible for the *in vivo* efficacy of JAK inhibitors in immune-inflammatory diseases. However, the overall clinical significance of the different JAK affinity profiles among the various JAK inhibitors has yet to be determined.

Prior to FDA-approval, upadacitinib was granted orphan drug designation for the treatment of pediatric juvenile idiopathic arthritis (JIA) in September 2015, and for the treatment of pediatric systemic juvenile idiopathic arthritis (SJIA) in August 2017. In December 2021, based on the results of a post-marketing safety study of tofacitinib (Xeljanz) showing increased risk of all-cause mortality, major adverse cardiovascular events, and cancer as compared to TNF blockers in certain RA patients, the FDA modified upadacitinib’s RA indication to require an inadequate response or intolerance to one or more TNF blockers. The Boxed Warning was also updated to include this additional safety information. Also, in December 2021, the FDA approved the new indication of treatment of adults with active psoriatic

arthritis who have had an inadequate response or intolerance to one or more TNF blockers. In January 2022, the FDA approved the new indication of treatment of adults and pediatric patients 12 years of age and older 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 are inadvisable. In March 2022, the FDA approved the new indication of treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers. In April 2022, the FDA approved the new indication of treatment of adults with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to one or more TNF blockers. In October 2022, the FDA approved the new indication of treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy. In May 2023, the FDA approved the new indication of treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to one or more TNF blockers. In April 2024, the FDA approved the new indication of treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (PJIA) who have had an inadequate response or intolerance to one or more TNF blockers. Also in April 2024, the indication for active psoriatic arthritis was expanded to include pediatric patient 2 years of age and older. Coinciding with these approvals, a new liquid formulation of upadacitinib, Rinvoq LQ, was also approved. Rinvoq LQ oral solution is not directly substitutable with Rinvoq extended-release tablets. In April 2025, the FDA approved a new indication for Rinvoq for the treatment of adults with giant cell arteritis (GCA). In October 2025, the FDA approved revisions to the indication for CD and UC. The updated indications now allow the use of Rinvoq for patients after they have received at least one approved systemic therapy in the event TNF blockers are clinically inadvisable.

RHEUMATOID DISORDERS

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that primarily affects the joints but can also damage extra-articular organs. The main goal of therapy is to achieve remission, but additional goals include decreased disease activity, prevention of systemic complications, and improved physical functioning. The choice of therapy depends on several factors, including the severity of disease activity when therapy is initiated and the response of the patient to prior therapeutic interventions. American College of Rheumatology (ACR) guidelines list the following guiding principles in the treatment of RA:

- RA requires early evaluation, diagnosis, and management
- Treatment decisions should follow a shared decision-making process
- Treatment decisions should be reevaluated within a minimum of 3 months based on efficacy and tolerability of the disease-modifying antirheumatic drug(s) (DMARDs) chosen
- Recommendations are limited to DMARDs approved by the US FDA for treatment of RA:
    - Conventional synthetic DMARDs (csDMARDs): hydroxychloroquine, sulfasalazine, methotrexate (MTX), leflunomide
    - Biologic DMARDs (bDMARDs): Tumor necrosis factor (TNF) inhibitors (e.g., etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (e.g.,

abatacept), Interleukin (IL)-6 receptor inhibitors (e.g., tocilizumab, sarilumab), anti-CD20 antibody* (e.g., rituximab)

*Recommendations referring to bDMARDs exclude rituximab unless patients have had an inadequate response to TNF inhibitors (in order to be consistent with FDA approval) or have a history of lymphoproliferative disorder for which rituximab is an approved therapy

  - Targeted synthetic DMARDs (tsDMARDs): Janus kinase (JAK) inhibitors (e.g., tofacitinib, baricitinib, upadacitinib)

- Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide
- Biosimilars are considered equivalent to FDA-approved originator bDMARDs
- Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modifications of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission)

ACR guidelines (2021) are broken down by previous treatment and disease activity:

- DMARD-naïve patients with moderate-to-high disease activity initial treatment:
  - MTX monotherapy is strongly recommended over hydroxychloroquine, sulfasalazine, bDMARDs monotherapy, tsDMARD monotherapy, or combination of MTX plus a non-TNF bDMARD or tsDMARD
  - MTX monotherapy is conditionally recommended over leflunomide, dual or triple csDMARD therapy, or combination MTX plus a TNF inhibitor
- DMARD-naïve patients with low disease activity initial treatment
  - Hydroxychloroquine is conditionally recommended over other csDMARDs
  - Sulfasalazine is conditionally recommended over MTX
  - MTX is conditionally recommended over leflunomide
- Initial therapy in csDMARD-treated patients, but MTX naïve, with moderate-to high disease activity:
  - MTX monotherapy is conditionally recommended over combination MTX and a bDMARD or tsDMARD
- Treatment modifications in patients treated with DMARDs who are not at target:
  - Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy for patients taking maximally tolerated doses of MTX who are not at target
  - Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target.

The European Alliance of Associations for Rheumatology (EULAR) guidelines for RA (2022 update) also recommend a treat-to-target approach in therapy. MTX is recommended as first line therapy and should be initiated as soon as the diagnosis of RA is made. If MTX is not clinically appropriate, then an alternative csDMARD should be used as part of the (first) treatment strategy. If initial csDMARD therapy does not produce adequate improvement after 3 months, another csDMARD may be added or switched

to as long as poor prognosis factors are absent. In the presence of poor prognosis factors, a bDMARD or JAK inhibitor should be added to csDMARD therapy. If treatment failure occurs with the initial bDMARD or JAK inhibitor, another bDMARD or JAK inhibitor should be considered. If a TNF- or IL-6 receptor inhibitor therapy was initially failed, patients may receive an agent with another mode of action or a second TNF- or IL-6 receptor inhibitor.

Initial dosing of MTX for RA should optimally be 15 mg once weekly, with the dose increased as tolerated and as needed to control signs and symptoms. A fast dose escalation of 5 mg/month to 25-30 mg/week has been associated with higher efficacy, but toxicity with this dosing regimen is a limiting factor. In the presence of sufficient folic acid supplementation, the MTX dose can be rapidly escalated to 25 mg once weekly. The MTX target dose is 25 mg weekly, or the highest tolerable dose.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Juvenile idiopathic arthritis (JIA) is arthritis that begins before the 16th birthday and persists for at least 6 weeks with other known conditions excluded. Polyarticular juvenile idiopathic arthritis (PJIA) is a subset of JIA. The ACR defines PJIA as arthritis in more than 4 joints during their disease course and excludes systemic JIA. Treatment goals are aimed at achieving clinically inactive disease and to prevent long-term morbidities, including growth disturbances, joint contractures and destruction, functional limitations, and blindness or visual impairment from chronic uveitis.

The American College of Rheumatology guidelines (2019) (ACR)/Arthritis Foundation recommend the following treatment approach for PJIA:

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are conditionally recommended as adjunct therapy
- Disease modifying antirheumatic drug (DMARD) therapy:
    - Methotrexate (MTX) is conditionally recommended over leflunomide and sulfasalazine
    - Subcutaneous MTX is conditionally recommended over oral MTX
- Intraarticular glucocorticoids are conditionally recommended as adjunct therapy and conditionally recommended for bridging only in patients with moderate to high disease activity
- Strongly recommend against chronic low-dose glucocorticoid use, irrespective of disease activity and/or risk factors
- Strongly recommend combination use of a DMARD and infliximab
- Initial therapy for all patients:
    - DMARD is strongly recommended over NSAID monotherapy
    - MTX monotherapy is conditionally recommended over triple DMARD therapy
    - DMARD is conditionally recommended over a biologic
    - Initial biologic therapy may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, hip), high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage
- Subsequent therapy:
    - Low disease activity:

        - Escalating therapy (e.g., intraarticular glucocorticoid injections, optimization of DMARD dose, trial of MTX if not already done, and adding or changing biologic agent)
    - Moderate to high disease activity:
        - Add a biologic to original DMARD over changing to a second DMARD or changing to triple DMARD therapy
        - Switch to a non- tumor necrosis factor (TNF) biologic if currently treated with first TNF-inhibitor ± DMARD over switching to another TNF-inhibitor (unless the patient had good initial response to first TNF-inhibitor)
        - TNF-inhibitor, abatacept, or tocilizumab (depending on prior biologics received) over rituximab after trial of second biologic

Psoriatic Arthritis (PsA)

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis (PS), most commonly presenting with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Active PsA is defined as symptoms at an unacceptably bothersome level as reported by the patient due to one of the following: actively inflamed joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and/or extraarticular manifestations such as uveitis or inflammatory bowel disease (IBD). Disease severity is based on the assessment of the level of disease activity at a given point in time, and the presence/absence of poor prognostic factors and long-term damage. Severe PsA is defined in the American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) guidelines for PsA and includes the presence of one or more of the following:

- Erosive disease
- Elevated markers of inflammation (e.g., erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) attributable to PsA
- Long-term damage that interferes with function (e.g., joint deformities, vision loss)
- Highly active disease that causes a major impairment in quality of life, such as:
    - Active PsA at many sites including dactylitis and enthesitis
    - Function-limiting PsA at a few sites
- Rapidly progressive disease

Treatment involves the use of a variety of interventions, including many agents used for the treatment of other inflammatory arthritis disorders, particularly spondyloarthritis and rheumatoid arthritis, and other management strategies of the cutaneous manifestations of psoriasis. Symptomatic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and local glucocorticoid injections. Only patients with very mild peripheral disease may sufficiently benefit from NSAIDs as monotherapy, and instead patients are typically treated with disease-modifying antirheumatic drugs (DMARDs) and/or biologics. Efficacy of DMARD and biologic therapies should be assessed 3 months after initiation, and if adequate improvement is not seen then the treatment regimen should be updated or changed. The ACR-NPF guidelines for PsA recommend a treat-to-target approach in therapy, regardless of disease activity, and treatment recommendations for active disease are as follows:

- Treatment naïve patients:

- First line options include oral small molecules (OSM), tumor necrosis factor (TNF) inhibitors, interleukin (IL)-17 inhibitors, and IL-12/23 inhibitors
    - OSM (i.e., methotrexate [MTX], sulfasalazine, cyclosporine, leflunomide, apremilast) should be considered if the patient does not have severe PsA, does not have severe PS, prefers oral therapy, has concern over starting a biologic, or has contraindications to TNF inhibitors
    - Biologics (e.g., TNF inhibitor, IL-17 inhibitor, IL-12/23 inhibitor) are recommended as a first line option in patients with severe PsA and/or severe PS

- Previous treatment with OSM and continued active disease:
    - Switch to a biologic (i.e., TNF inhibitor, IL-17 inhibitor, IL-12/23 inhibitor); recommended over switching to a different OSM
        - Biologic monotherapy is conditionally recommended over biologic plus MTX combination therapy
    - Switch to a different OSM (except apremilast) OR add on apremilast to current OSM therapy; recommended over adding another OSM
    - Add another OSM (except apremilast) to current OSM therapy; may consider for patients that have exhibited partial response to current OSM
    - Switch to apremilast monotherapy; may be considered instead of adding apremilast to current OSM therapy if the patient has intolerable side effects with the current OSM
- Previous treatment with a biologic and continued active disease:
    - Switch to another biologic (e.g., TNF inhibitor, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, or tofacitinib) as monotherapy
    - Add MTX to the current biologic; may consider adding MTX in patients with a partial response to current biologic therapy

The European Alliance of Associations for Rheumatology (EULAR) guidelines for PsA (2023 update) also recommend a treat-to-target approach in therapy. MTX (preferred) or another conventional synthetic disease-modifying antirheumatic drug (csDMARD) (e.g., sulfasalazine, leflunomide) should be used for initial therapy. If the treatment target is not achieved with a csDMARD, a biologic should be initiated with preference of product being based on patient specific disease characteristics. Biologics include TNF inhibitors, IL-12/23 inhibitors, IL-17A inhibitors, IL-17A/F inhibitors, IL-23 inhibitors, and cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) analogs. No order of preference of biologics is provided since none have demonstrated superiority for joint involvement, however, CTLA4 analogs are least preferred due to limited efficacy in clinical trials. The use of a Janus kinase (JAK) inhibitor (e.g., tofacitinib, upadacitinib) may be used after failure of a biologic or if biologics are not clinically appropriate for the patient. However, careful consideration should be applied prior to using a JAK inhibitor due to the increased risk of cardiovascular and malignancy events in older patients with RA and cardiovascular risk factors. A phosphodiesterase-4 (PDE4) inhibitor (i.e., apremilast) may be considered in patients with mild disease and an inadequate response to at least one csDMARD, in whom neither a biologic nor a JAK inhibitor is appropriate. Patients with an inadequate response to a biologic or JAK inhibitor may switch to a different drug within the same class or switch to a different mode of action. Adding MTX to a biologic may increase drug survival by limiting the development of antidrug antibodies, especially for TNF inhibitors.

Ankylosing spondylitis (AS)

Ankylosing spondylitis (AS) is a form of chronic inflammatory arthritis characterized by sacroiliitis, enthesitis, and a marked propensity for sacroiliac joint and spinal fusion. AS is distinguished by universal involvement with sacroiliac joint inflammation or fusion and more prevalent spinal ankylosis. Goals of treatment for AS are to reduce symptoms, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, and decrease disease complications. The mainstays of treatment have been nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise/physical therapy.

NSAIDs are used as first line therapy for patients with active AS, with continuous treatment with NSAIDs being preferred. In patients with stable disease, NSAIDs may be used on-demand to decrease the risk of adverse effects with long term use. No particular NSAID is recommended as a preferred option. Biologics should be used in patients who continue to have persistently high disease activity despite NSAIDs. Failure of standard treatment with NSAIDs can be defined as a lack of response (or intolerance) to at least 2 NSAIDs after at least a 4-week duration of therapy in total.

Tumor necrosis factor (TNF) inhibitors or interleukin (IL)-17 inhibitors are recommended as initial biologic therapy. Other present comorbidities (e.g., inflammatory bowel disease, psoriasis, uveitis) can help guide selection of the initial biologic agent/drug class. Patients who have an inadequate response to a TNF inhibitor or IL-17 inhibitor may switch to a biologic of the other drug class, or switch to a Janus kinase (JAK) inhibitor. Patients with secondary failure to a biologic (presence of antidrug antibodies) may switch to another biologic of the same or different mode of action.

Systemic glucocorticoids should generally not be used in the treatment of AS. Short-term glucocorticoid injections may be used in select patients with peripheral signs and symptoms. Conventional disease-modifying antirheumatic drugs (cDMARDs) (e.g., methotrexate, sulfasalazine, leflunomide) are not recommended as treatment due to their lack of efficacy. However, sulfasalazine may be considered in patients with peripheral arthritis.

INFLAMMATORY BOWEL DISEASE

Crohn's Disease (CD)

Crohn's disease (CD) is a chronic inflammatory bowel disease with genetic, immunologic, and environmental influences. It can affect any portion of the gastrointestinal tract but involves the small intestine and proximal colon most often. The most common symptom is diarrhea, but abdominal pain, fatigue, fever, weight loss, and vomiting are also prevalent. Symptoms typically occur as a chronic, intermittent course, with only a minority of patients having continuously active symptomatic disease or a prolonged remission. In most cases, CD is a chronic, progressive, destructive disease. Early diagnosis and management of CD can lead to better outcomes and less negative impact on quality of life.

Patients are considered to have moderate to severe disease if they have failed to respond to treatment for mild to moderate disease, or if they present with more prominent symptoms of CD. Inflammation-related biomarkers are more likely to be abnormal, and greater endoscopic disease burden is typical. This includes larger or deeper ulcers, strictures, or extensive areas of disease and/or evidence of stricturing, penetrating, or perianal disease. The International Organization for the Study of Inflammatory Bowel Diseases characterizes patients with severe disease as having at least 10 loose stools per day, daily abdominal pain, presence of anorectal symptoms, systemic corticosteroid use

within the prior year, lack of symptomatic improvement despite prior exposure to biologics and/or immunosuppressive agents, or significant impact of the disease on activities of daily living. They are also at a high risk for adverse disease-related complications, including surgery, hospitalization, and disability, based on a combination of structural damage, inflammatory burden, and impact of quality of life. Patients with severe disease may have large or deep mucosal lesions on endoscopy or imaging, presence of fistula and/or perianal abscess, presence of strictures, prior intestinal resections, presence of a stoma, and/or extensive disease (e.g., involvement of long bowel segments, pancolitis).

The choice of therapy in CD is dependent on the anatomic location of the disease, the severity of disease, and whether the treatment is needed to induce remission or maintain remission. The goal of treatment for induction of remission is to achieve clinical response and control of inflammation within 3 months of treatment initiation. After inducing clinical remission, patients should be transitioned to steroid-sparing maintenance therapy. In the absence of immunomodulator or biologic treatment, corticosteroid dependency and/or resistance occurs in up to half of patients. In general, the drug(s) used for induction of remission should be continued as maintenance therapy, with the exception of corticosteroids.

The American Gastroenterological Association (AGA) 2021 guideline provides the following recommendations and guidance:

- Biologic therapy:
    - The AGA suggest early introduction with a biologic, with or without an immunomodulator, rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids (Conditional recommendation, low certainty of evidence)
        - Earlier therapy with a biologic may result in overtreating some patients and potentially exposing them to treatment-related risks and costs with limited benefit. However, step-up therapy comes with a potential risk of harm from disease progression related to inadequate disease therapy.
    - Anti-tumor necrosis factor (TNF) (i.e., infliximab or adalimumab) and ustekinumab are recommended over no treatment for the induction and maintenance of remission
    - Vedolizumab is suggested over no treatment for the induction and maintenance of remission
    - AGA suggests against the use of natalizumab over no treatment for the induction and maintenance of remission
    - Patients naïve to biologic therapy, the AGA recommends infliximab, adalimumab, or ustekinumab over certolizumab pegol and suggests the use of vedolizumab over certolizumab pegol for the induction of remission
    - Patients with primary non-response to anti-TNF, the AGA recommends ustekinumab and suggests vedolizumab for induction of remission
    - Patients with secondary non-response to infliximab, the AGA recommends use of adalimumab or ustekinumab and suggests the use of vedolizumab for the induction of remission (if adalimumab was the first line drug, there is indirect evidence to suggest using infliximab as a second-line agent)
- Corticosteroid therapy:

    - Corticosteroids are suggested over no treatment for the induction of remission, and are recommended against for maintenance of remission
        - In patients with CD involving the distal ileum and/or ascending colon who are more concerned about systemic corticosteroids and less concerned about the lower efficacy, they may reasonably choose budesonide over systematic corticosteroids for inducing remission
- Disease modifying antirheumatic drug (DMARD) therapy:
    - Patients in corticosteroid induced remission or with quiescent moderate to severe CD, the AGA suggests thiopurines for maintenance of remission
    - Subcutaneous or intramuscular methotrexate are suggested over no treatment for the induction and maintenance of remission
    - The AGA recommends against the use of 5-aminosalicylates or sulfasalazine over no treatment for the induction or maintenance of remission
    - The AGA suggests against the use of thiopurines over no treatment for achieving remission and recommends biologic drug monotherapy over thiopurine monotherapy for induction of remission
    - The AGA suggests against the use of oral methotrexate monotherapy over no treatment for the induction and maintenance of remission
- Combination therapy:
    - Patients that are naïve to biologics and immunomodulators, the AGA suggest use of infliximab in combination with thiopurines over infliximab monotherapy for the induction and maintenance of remission (combination infliximab with methotrexate may be more effective over infliximab monotherapy)
    - Patients that are naïve to biologics and immunomodulators, the AGA suggest use of adalimumab in combination with thiopurines over adalimumab monotherapy for the induction and maintenance of remission (combination adalimumab with methotrexate may be more effective over adalimumab monotherapy)
    - No recommendations are being made regarding the use of ustekinumab or vedolizumab in combination with thiopurines or methotrexate over biologic monotherapy for induction or maintenance or remission

The American College of Gastroenterology (ACG) 2025 guideline provides the following recommendations and guidance:

- Biologic therapy:
    - Biologic agents are effective for treating patients with active CD and previous inadequate response to corticosteroids, thiopurines, and/or methotrexate
    - Suggest against requiring failure of conventional therapy before initiation of advanced therapy for the management of CD (conditional recommendation, low level of evidence)
        - The risk of adverse effects and high cost of biologic agents may not be justifiable in a lower risk population
    - Recommend the following drugs for induction and maintenance of remission for moderately to severely active CD:

        - Anti-TNF agents (i.e., infliximab, adalimumab, certolizumab), vedolizumab, ustekinumab, risankizumab, mirikizumab, guselkumab
    - Recommend combination therapy of intravenous infliximab with immunomodulators (thiopurines) as compared with treatment with either immunomodulators alone or intravenous infliximab alone in patients with CD who are naïve to those agents
    - Recommend the use of risankizumab as compared with ustekinumab in patients with moderate to severe CD and prior exposure to anti-TNF therapy
    - Biosimilar infliximab, adalimumab, and ustekinumab are effective treatments for patients with moderate-to-severe CD and can be used for de novo induction and maintenance therapy
    - There are data to support the safety and efficacy of transitioning or switching to biosimilar infliximab or adalimumab for patients with CD in stable disease maintenance
- Janus kinase (JAK) inhibitor therapy:
    - Recommend upadacitinib use for induction and maintenance of remission for patients with moderate-to-severe CD who have previously been exposed to anti-TNF agents
- Corticosteroid therapy:
    - Recommend oral corticosteroids for short-term induction of remission in patients with moderately to severely active CD
        - Recommend controlled ileal release budesonide at a dose of 9 mg daily for induction of symptomatic remission in patients with mildly to moderately active ileocecal CD
    - Corticosteroids should not be used for maintaining remission, and their use should not exceed 3 continuous months without attempting to introduce a steroid-sparing agent (such as an immunomodulator)
- DMARD therapy:
    - Recommend against azathioprine or 6-mercaptopurine for induction of remission in moderately to severely active CD
        - Due to their slow onset of action of 8 to 12 weeks, thiopurines are not effective agents for induction of remission
    - Suggest azathioprine or 6-mercaptopurine for maintenance of remission in patients with moderately to severely active CD who had induction of remission with corticosteroids
    - Suggest methotrexate (up to 25 mg once weekly intramuscular or subcutaneous) for maintenance of remission in patients with moderately to severely active CD who had induction of remission with corticosteroids
    - Azathioprine, 6-mercaptopurine, or methotrexate may be used in the treatment of active CD and as adjunctive therapy for reducing immunogenicity associated with anti-TNF therapy

Ulcerative Colitis (UC)

Ulcerative colitis (UC) is a chronic inflammatory bowel disease affecting the large intestine. It typically starts with inflammation of the rectum, but often extends proximally to involve additional areas of the colon. The most common symptom is bloody diarrhea, but urgency, tenesmus, abdominal pain, malaise,

weight loss, and fever can also be associated. UC commonly has a gradual onset and will present with periods of spontaneous remission and subsequent relapses.

Disease severity is based on patient-reported outcomes (e.g., bleeding, bowel habits, bowel urgency), inflammatory burden (e.g., endoscopic assessment, inflammatory markers), disease course, and disease impact. Commonly assessed symptoms include frequency and timing of bowel movements, rectal bleeding, bowel urgency, abdominal pain, bowel cramping, and weight loss. Poor prognostic factors include less than 40 years of age at diagnosis, extensive colitis, severe endoscopic disease, hospitalization for colitis, elevated C-reactive protein (CRP), and low serum albumin. Therapeutic management in UC should be guided by the extent of bowel involvement, assessment of disease activity (i.e., quiescent, mild, moderate, or severe), and disease prognosis. Treatment response should be evaluated 12 weeks after initiation of therapy to confirm efficacy and safety.

The American College of Gastroenterology (ACG) published recommendations and guidance (2025) for the management of moderate-to-severe UC:

<u>General treatment information</u>:

- Patients with mildly to moderately active UC and a number of prognostic factors associated with an increased risk of hospitalization or surgery should be treated with therapies for moderate-to-severe disease
- Patients with mildly to moderately active UC who are not responsive (or are intolerant) to 5-aminosalicylate (5-ASA) therapies (e.g., balsalazide, mesalamine, sulfasalazine) should be treated as patients with moderate-to-severe disease

<u>Corticosteroid therapy</u>:

- In patients with moderately active UC, recommend oral budesonide multi-matrix system (MMX) for induction of remission
    - In patients with moderately active UC, consider nonsystemic corticosteroids such as budesonide MMX before the use of systemic therapy
- Recommend oral systemic corticosteroids to induce remission in UC of any extent
    - In patients with severely active UC, consider systemic corticosteroids rather than topical corticosteroids
- Recommend against systemic, budesonide MMX, or topical corticosteroids for maintenance of remission

<u>Disease modifying antirheumatic drug (DMARD) therapy</u>:

- Recommend against monotherapy with thiopurines or methotrexate for induction of remission
- 5-ASA therapy could be used as monotherapy for induction of moderately but not severely active UC
- 5-ASA therapy for maintenance of remission is likely not as effective in prior severely active UC as compared with prior moderately active UC
- Suggest thiopurines for maintenance of remission in patients now in remission due to corticosteroid induction
- Suggest against using methotrexate for maintenance of remission

Biologic/advanced therapy:

- Recommend the following drugs for induction of remission and continuing the same drug for maintenance of remission:
    - Anti-tumor necrosis factor (TNF) agents (e.g., infliximab, adalimumab, golimumab), ustekinumab, guselkumab, mirikizumab, risankizumab, vedolizumab, tofacitinib, upadacitinib, sphingosine-1-phosphate (S1P) receptor modulators (e.g., ozanimod, etrasimod)
    - Most clinical trials and available data demonstrate a benefit of using the steroid-sparing therapy that induces remission to maintain that remission
- When infliximab is used as induction therapy, recommend combination therapy with a thiopurine
    - Data on combination anti-TNF and immunomodulators in moderately to severely active UC only exist for infliximab and thiopurines
- Infliximab is the preferred anti-TNF therapy for patients with moderately to severely active UC
- Recommend vedolizumab as compared to adalimumab for induction and maintenance of remission
- Patients who are primary nonresponders to an anti-TNF (defined as lack of therapeutic benefit after induction and despite sufficient serum drug concentrations) 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
- Biosimilars to anti-TNF therapies and to ustekinumab are acceptable substitutes for originator therapies. Delays in switching should not occur and patients and clinicians should be notified about such changes

The American Gastroenterology Association (AGA) published recommendations and guidance (2018) for the management of mild-to-moderate UC:

- In patients with moderate disease activity, suggest using high dose mesalamine (greater than 3 g/day) with rectal mesalamine for induction of remission and maintenance of remission
- Add either oral prednisone or budesonide MMX in patients that are refractory to optimized oral and rectal 5-ASA, regardless of disease extent
- If progression to moderate-to-severe disease activity occurs, or if the patient is at high risk for colectomy despite therapy, consider escalating to treatment for moderate-to-severe disease with immunomodulators and/or biologics

The American Gastroenterology Association (AGA) published recommendations and guidance (2024) for the management of moderate-to-severe UC:

General treatment information:

- Suggest early use of advanced therapy (e.g., biologics, ozanimod, etrasimod), with or without immunomodulator therapy (e.g., thiopurines), rather than treatment with 5-ASA and a gradual step up to biologic/immunomodulator therapy after 5-ASA treatment failure (conditional recommendation, very low certainty of evidence)
    - Patients with less severe disease or those who place a higher value on the safety of 5-ASA therapy over the efficacy of immunosuppressives may reasonably choose gradual step therapy with 5-ASA therapy

DMARD therapy:

- Suggest against using thiopurine monotherapy for inducing remission
- Suggest thiopurine monotherapy may be used for maintaining remission typically induced with corticosteroids
- Suggest against using methotrexate monotherapy for inducing or maintaining remission

Advanced therapy:

- Recommend using one of the following advanced therapies over no treatment:
    - Infliximab, golimumab, vedolizumab, tofacitinib, upadacitinib, ustekinumab, ozanimod, etrasimod, risankizumab, guselkumab
- Suggest using one of the following advanced therapies over no treatment:
    - Adalimumab, filgotinib*, mirikizumab (*not currently approved by the Food and Drug Administration)
- Biosimilars of infliximab, adalimumab, and ustekinumab can be considered equivalent to their originator drug in their efficacy
- Suggest the use of infliximab in combination with an immunomodulator over infliximab or an immunomodulator alone
- Suggest the use of adalimumab or golimumab in combination with an immunomodulator over adalimumab, golimumab or immunomodulator monotherapy

Advanced therapy-naïve patients (first-line therapy):

- Suggest that a higher or intermediate efficacy medication be used rather than a lower efficacy medication
    - Higher efficacy: infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib, risankizumab, guselkumab
    - Intermediate efficacy: golimumab, ustekinumab, tofacitinib, filgotinib, mirikizumab
    - Lower efficacy: adalimumab

Prior exposure to one or more advanced therapies, particularly TNF antagonists:

- Suggest that a higher or intermediate efficacy medication be used rather than a lower efficacy medication
    - Higher efficacy: tofacitinib, upadacitinib, ustekinumab
    - Intermediate efficacy: filgotinib, mirikizumab, risankizumab, guselkumab
    - Lower efficacy: adalimumab, vedolizumab, ozanimod, etrasimod

DERMATOLOGICAL DISORDERS

Atopic Dermatitis

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, pruritic inflammatory dermatosis affecting up to 25% of children and approximately 7% of adults. AD follows a relapsing course and is

associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and/or asthma. Onset is most common between 3 and 6 months of age, with approximately 60% of patients developing the eruption in the first year of life and 90% by age 5. While the majority of affected individuals have resolution of disease by adulthood, 10 to 30% do not, and a smaller percentage first develop symptoms as adults. AD has a complex pathogenesis involving genetic, immunologic, and environmental factors, which lead to a dysfunctional skin barrier and dysregulation of the immune system. Clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification. These clinical findings vary by patient age and chronicity of lesions. Pruritus is a hallmark of the condition that is responsible for much of the disease burden borne by patients and their families. Typical patterns include facial, neck and extensor involvement in infants and children, flexure involvement in any age group, with sparing of groin and axillary regions.

Goals of treatment are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and minimize therapeutics risks. Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with topical emollient/moisturizer use and conventional topical therapies (including corticosteroids and calcineurin inhibitors). Moisturizers reduce signs, symptoms, and inflammation in AD, and can improve severity while also increasing time between flares. Moisturizers are considered generally safe and are strongly recommended to be used as part of a treatment regimen for AD, either as monotherapy or as concurrent use with pharmacologic treatments.

Topical therapies remain the mainstay of treatment due to their proven track record and generally favorable safety profile. They can be utilized individually or in combination with other topical, physical, and/or systemic treatments; as different classes of treatment have different mechanisms of action, combining therapies allows for the targeting of AD via multiple disease pathways. The American Academy of Dermatology (AAD) strongly recommends the following topical agents:

- Topical corticosteroids (TCS)
- Calcineurin inhibitors (TCIs) (e.g., tacrolimus, pimecrolimus)
- Topical phosphodiesterase (PDE)-4 inhibitors (e.g., crisaborole) [mild to moderate AD]
- Topical Janus kinase (JAK) inhibitors (e.g., ruxolitinib) [mild to moderate AD]

TCS are the most commonly utilized FDA-approved therapies in AD and are commonly used as first-line treatment for mild-to severe dermatitis in all skin regions. TCS target a variety of immune cells and suppress the release of proinflammatory cytokines. High to very high (super) potency TCS can be used to control flares and treat severe disease, while medium potency TCS are utilized for longer courses and as maintenance therapy. Lower potency TCS may be used, and it is important to consider the anatomical site (i.e., using lower potency agents on the face, neck, genitals, and body folds) and severity of the disease when choosing a steroid potency. Clinical trials assessing efficacy generally had a duration of 2 to 6 weeks, and response to TCS therapy should be evaluated by week 4 in clinical practice. Most studies of TCS in AD management involve twice daily application, but some studies (particularly for potent TCS) suggest once daily use may be sufficient. Traditionally, TCS were stopped once AD signs and symptoms of an AD flare were controlled. Maintenance in between AD flares with once to twice weekly use of TCS is another approach.

TCIs are a safe anti-inflammatory option for mild-to-severe AD, particularly when there is concern for adverse events secondary to corticosteroid use. Both tacrolimus and pimecrolimus have been shown to

be effective in treating AD, but pimecrolimus may be more appropriate for patients who have milder disease or are sensitive to local reactions. Prescribing information for pimecrolimus cream and tacrolimus ointment indicate evaluation after 6 weeks if symptoms of AD do not improve for adults and pediatrics.

When AD is more severe or refractory to topical treatment, advanced treatment with phototherapy or systemic medications can be considered. Phototherapy is conditionally recommended by the AAD as a treatment for AD based on low certainty evidence. The AAD strongly recommends the following systemic therapies:

- Monoclonal antibodies (biologics) (e.g., dupilumab, tralokinumab)
- JAK inhibitors (e.g., upadacitinib, abrocitinib, baricitinib)

In a change from the 2014 AAD AD guidelines, the use of systemic antimetabolites such as methotrexate, immunosuppressants such as systemic corticosteroids, mycophenolate mofetil, azathioprine, and cyclosporine are now conditionally recommended for AD only in a small number of select patients due to low or very low certainty of evidence and need for monitoring. The most favored first-line systemic is dupilumab.

There is no clear consensus on how to operationalize a definition of the FDA indication for treatment of patients with "moderate to severe" AD. The severity of AD can vary substantially over time and, from a patient's perspective, can include a complex combination of intensity of itch, location, body surface area (BSA) involvement, and degree of skin impairment. Given the variability of patient phenotype and lack of familiarity among clinicians with scoring systems used in clinical trials, it is advisable to create a broad clinically relevant definition inclusive of multiple specific measures of disease intensity for example:

- One of the following:
  - Affected BSA greater than or equal to 10%
  - Investigator Global Assessment (IGA) greater than or equal to 3
  - Eczema Area and Severity Index (EASI) greater than or equal to 16

  OR
- One of the following:
  - Affected BSA greater than or equal to 10%
  - Involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds)
  - Severe itch that has been unresponsive to topical therapies

OTHER DISORDERS

Giant Cell Arteritis (GCA)

Giant cell arteritis (GCA) is a blood vessel disease that predominantly affects medium to large arteries in individuals older than 50 years of age, causing clinical manifestations in both cranial and extracranial locations. The cranial phenotype is characterized by headache, jaw claudication, and visual disturbance or loss. The extracranial phenotype is characterized by musculoskeletal involvement with symptoms

associated with polymyalgia rheumatica, such as pain, stiffness, and limited range of motion around the shoulders, neck, and hips. Treatment should begin as soon as the diagnosis is made to prevent loss of vision or blindness.

The American College of Rheumatology/Vasculitis Foundation guidelines (2021) recommend high-dose systemic glucocorticoids as the mainstay of therapy for GCA. The guidelines provide the following recommendations for the management of GCA:

- Patients with newly diagnosed active GCA with visual symptoms/loss or critical cranial ischemia:
  - High dose IV pulse corticosteroids followed by high dose oral corticosteroids with or without a non-corticosteroid immunosuppressive agent (i.e., methotrexate or tocilizumab)
  - Taper oral corticosteroids in patients that achieve remission
  - Consider adding on or changing non-corticosteroid immunosuppressive agent in patients that have not achieved remission
- Patients with newly diagnosed active GCA without visual symptoms/loss or critical cranial ischemia:
  - High dose oral corticosteroids with or without a non-corticosteroid immunosuppressive agent (i.e., methotrexate or tocilizumab)
  - Taper oral corticosteroids in patients that achieve remission
  - Consider adding on or changing non-corticosteroid immunosuppressive agent in patients that have not achieved remission

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

NOTE: The list of self-administered products with prerequisites for certain indications can be found at Preferred Agents and Drug List.

Initiation of upadacitinib (Rinvoq) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. **ONE** of the following ("a", "b", or "c"):
   a. The member has been treated with upadacitinib (starting on samples is not approvable) within the past 90 days
   b. The prescriber states the member has been treated with upadacitinib (starting on samples is not approvable) within the past 90 days **AND** is at risk if therapy is changed
   c. **BOTH** of the following ('i" and "ii"):
      i. Upadacitinib will be used for the treatment of an indication listed in Table 1, and **ALL** of the indication-specific criteria are met

ii. **EITHER** of the following if the member has an FDA-approved indication ("I" or "II")

I. The member's age is within FDA labeling for the requested indication for upadacitinib

II. The prescriber has provided information in support of using upadacitinib for the member's age for the requested indication

2. If the member has a diagnosis of atopic dermatitis, then **BOTH** of the following ("a" and "b"):
   a. The member is currently treated with topical emollients and practicing good skin care
   b. The member will continue the use of topical emollients and good skin care practices in combination with upadacitinib
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., allergist, dermatologist, or immunologist for AD, gastroenterologist for CD or UC, rheumatologist for AS, GCA, nr-axSpA, PJIA, PsA or RA) or the prescriber has consulted with a specialist in the area of the member's diagnosis
4. Member does **NOT** have any FDA labeled contraindications to upadacitinib
5. Member will **NOT** be using upadacitinib in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), and Xeljanz/Xeljanz XR (tofacitinib)]; Otezla/Otezla XR (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
6. **ANY** of the following ("a". "b", "c", or "d"):
   a. **EITHER** of the following based on indication:
      i. Atopic dermatitis - the dosage of upadacitinib ER tablet does not exceed 30 mg once daily
         - QL: 15 mg tablet - 1 tablet/day
         - QL: 30 mg tablet – 1 tablet/day
      ii. Crohn's disease

   a. Induction - the dosage of upadacitinib ER tablet does not exceed 45 mg once daily for 12 weeks
      - QL: 45 mg tablet – 84 tablets/365 days

   b. Maintenance - the dosage of upadacitinib ER tablet does not exceed 30 mg once daily
      - QL: 15 mg tablet - 1 tablet/day
      - QL: 30 mg tablet – 1 tablet/day

      iii. Psoriatic arthritis, and polyarticular juvenile idiopathic arthritis - the dosage does not exceed the following:

   a. Upadacitinib ER tablet - 15 mg once daily
      - QL: 15 mg tablet - 1 tablet/day

   b. Upadacitinib oral solution - the following based on member weight:
      - 10 kg to less than 20 kg - 3 mg (3 mL oral solution) twice daily
        - QL: 1 mg/mL oral solution - 180 mL/30 days

- 20 kg to less than 30 kg - 4 mg (4 mL oral solution) twice daily
  - QL: 1 mg/mL oral solution - 240 mL/30 days
- 30 kg and greater - 6 mg (6 mL oral solution) twice daily
  - QL: 1 mg/mL oral solution - 360 mL/30 days

iv. Ulcerative colitis

a. Induction - the dosage of upadacitinib ER tablet does not exceed 45 mg once daily for 8 weeks
   - QL: 45 mg tablet – 56 tablets/365 days

b. Maintenance - the dosage of upadacitinib ER tablet does not exceed 30 mg once daily
   - QL: 15 mg tablet - 1 tablet/day
   - QL: 30 mg tablet – 1 tablet/day

v. Other indications - the dosage of upadacitinib ER tablet does not exceed 15 mg once daily
- QL: 15 mg tablet - 1 tablet/day

b. The member has an FDA labeled indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):

i. The requested quantity (dose) does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit

ii. **ALL** of the following ("1", "2", and "3"):

1. The requested quantity (dose) exceeds the FDA maximum labeled dose for the requested indication
2. The member has tried and had an inadequate response to at least a 3-month trial of the maximum FDA labeled dose for the requested indication (medical records required)
3. **EITHER** of the following ("a" or "b"):
   a. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit
   b. The requested quantity (dose) exceeds the maximum FDA labeled dose **AND** the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

c. The member has a compendia supported indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):

i. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit

ii. The requested quantity (dose) exceeds the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened

dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

d. The member does **NOT** have an FDA labeled indication **NOR** a compendia supported indication for the requested agent, **AND BOTH** of the following ("i" and "ii"):
   i. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
   ii. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

Approval duration: 6 months for atopic dermatitis and 12 months for all other indications (for CD and UC the 45 mg induction dose is approved for 12 weeks and 8 weeks, respectively, followed by the maintenance dosing approved for the remaining 40 or 44 weeks)

Table 1

Diagnosis	**Criteria**
Moderately to severely active rheumatoid arthritis (RA)	**BOTH** of the following: 1. **ONE** of the following: a. The member has tried and had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) after at least a 3-month duration of therapy **OR** b. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA for at least 3 months **OR** c. The member has an intolerance or hypersensitivity to **ONE** conventional agent (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** d. The member has an FDA labeled contraindication to **ALL** conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** e. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of RA **AND**

	2. **ANY** of the following: a. The member has tried and had an inadequate response to at least **ONE** TNF inhibitor for RA after at least a 3-month duration of therapy [preferred TNF inhibitors include - Adalimumab-aaty, Adalimumab-adaz, Enbrel (etanercept), Hadlima (adalimumab-bwwd), Humira (adalimumab), and Simlandi (adalimumab-ryvk)] **OR** b. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to therapy with **ONE** TNF inhibitor for RA **OR** c. The member has an FDA labeled contraindication to **ALL** TNF inhibitors for RA **OR** d. **ALL** TNF inhibitors are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried products for the requested indication
Active psoriatic arthritis (PsA)	**BOTH** of the following: 1. **ONE** of the following: a. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., cyclosporine, leflunomide, methotrexate, sulfasalazine) used in the treatment of PsA after at least a 3-month duration of therapy **OR** b. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of PsA **OR** c. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of PsA **OR** d. The member has severe active PsA (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to PsA, long-term damage that interferes with function [i.e., joint deformities, vision loss], rapidly progressive) **OR** e. The member has concomitant severe psoriasis (PS) (e.g., greater than 10% body surface area involvement, occurring on select

	locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) **OR** f. The member's medication history indicates use of another biologic immunomodulator agent **OR** Otezla/Otezla XR that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PsA **AND** 2. **ANY** of the following: a. The member has tried and had an inadequate response to at least **ONE** TNF inhibitor for PsA after at least a 3-month duration of therapy [preferred TNF inhibitors include - Adalimumab-aaty, Adalimumab-adaz, Enbrel (etanercept), Hadlima (adalimumab-bwwd), Humira (adalimumab), and Simlandi (adalimumab-ryvk)] **OR** b. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to therapy with **ONE** TNF inhibitor for PsA **OR** c. The member has an FDA labeled contraindication to **ALL** TNF inhibitors for PsA **OR** d. **ALL** TNF inhibitors are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication
Moderate-to-severe atopic dermatitis (AD)	**BOTH** of the following ("1" and "2"): 1. **ONE** of the following: a. The member has at least 10% body surface area involvement **OR** b. The member has involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) **OR** c. The member has an Eczema Area and Severity Index (EASI) score of greater than or equal to 16 **OR** d. The member has an Investigator Global Assessment (IGA) score of greater than or equal to 3

	AND 2. **EITHER** of the following ("a" or "b"): a. **BOTH** of the following ("i" and "ii"): i. **ONE** of the following: • The member has tried and had an inadequate response to **ONE** at least medium-potency topical corticosteroid used in the treatment of AD after at least a 4-week duration of therapy **OR** • The member has an intolerance or hypersensitivity to **ONE** at least medium- potency topical corticosteroid used in the treatment of AD **OR** • The member has an FDA labeled contraindication to **ALL** medium-, high-, and super-potency topical corticosteroids used in the treatment of AD **AND** ii. **ONE** of the following: • The member has tried and had an inadequate response to **ONE** topical calcineurin inhibitor (e.g., Elidel/pimecrolimus, Protopic/tacrolimus) used in the treatment of AD after at least a 6-week duration of therapy **OR** • The patient has an intolerance or hypersensitivity to **ONE** topical calcineurin inhibitor **OR** • The patient has an FDA labeled contraindication to **ALL** topical calcineurin inhibitors **OR** b. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of AD
Moderately to severely active ulcerative colitis (UC)	**BOTH** of the following: 1. **ONE** of the following: a. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine,

	sulfasalazine) used in the treatment of UC after at least a 3-month duration of therapy **OR** b. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of UC **OR** c. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of UC **OR** d. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of UC **AND** 2. **ANY** of the following: a. The member has tried and had an inadequate response to at least **ONE** preferred product after at least a 3-month duration of therapy **OR** b. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to at least **ONE** preferred product **OR** c. The member has an FDA labeled contraindication to **ALL** preferred products **OR** d. **ALL** preferred products are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried products for the requested indication **The preferred UC products are:** • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Selarsdi (ustekinumab-aekn) • Simlandi (adalimumab-ryvk)

	• Simponi (golimumab) • Skyrizi (risankizumab-rzaa) • Stelara (ustekinumab) • Steqeyma (ustekinumab-stba) • Tremfya (guselkumab) • Xeljanz/Xeljanz XR (tofacitinib) • Yesintek (ustekinumab-kfce)
Moderately to severely active Crohn's disease (CD)	**BOTH** of the following: 1. **ONE** of the following: a. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., 6-mercaptopurine, azathioprine, corticosteroids [e.g., prednisone, budesonide EC capsule], methotrexate) used in the treatment of CD after at least a 3-month duration of therapy **OR** b. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of CD **OR** c. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of CD **OR** d. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of CD **AND** 2. **ANY** of the following: a. The member has tried and had an inadequate response to at least **ONE** preferred product after at least a 3-month trial **OR** b. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to at least **ONE** preferred product **OR** c. The member has an FDA labeled contraindication to **ALL** preferred products

	OR d. **ALL** preferred products are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried products for the requested indication **The preferred CD products are:** • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Selarsdi (ustekinumab-aekn) • Simlandi (adalimumab-ryvk) • Skyrizi (risankizumab) • Stelara (ustekinumab) • Steqeyma (ustekinumab-stba) • Tremfya (guselkumab) • Yesintek (ustekinumab-kfce)
Active ankylosing spondylitis (AS)	**BOTH** of the following: 1. **ONE** of the following: a. The member has tried and had an inadequate response to **TWO** different NSAIDs used in the treatment of AS after at least a 4-week TOTAL duration of therapy **OR** b. The member has tried and had an inadequate response to **ONE** NSAID used in the treatment of AS after at least a 4-week duration of therapy **AND** an intolerance or hypersensitivity to **ONE** additional NSAID used in the treatment of AS **OR** c. The member has an intolerance or hypersensitivity to **TWO** different NSAIDs used in the treatment of AS **OR** d. The member has an FDA labeled contraindication to **ALL** NSAIDs used in the treatment of AS **OR** e. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in

	DrugDex with 1 or 2a level of evidence or AHFS for the treatment of AS **AND** 2. **ANY** of the following: a. The member has tried and had an inadequate response to at least **ONE** TNF inhibitor for AS after at least a 3-month duration of therapy [preferred TNF inhibitors include - Adalimumab-aaty, Adalimumab-adaz, Enbrel (etanercept), Hadlima (adalimumab-bwwd), Humira (adalimumab), and Simlandi (adalimumab-ryvk)] **OR** b. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to therapy with **ONE** TNF inhibitor for AS **OR** c. The member has an FDA labeled contraindication to **ALL** TNF inhibitors for AS **OR** d. **ALL** TNF inhibitors are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication
Active non-radiographic axial spondyloarthritis (nr-axSpA)	**BOTH** of the following: 1. **ONE** of the following a. The member has tried and had an inadequate response to **TWO** different NSAIDs used in the treatment of nr-axSpA after at least a 4-week TOTAL duration of therapy **OR** b. The member has tried and had an inadequate response to **ONE** NSAID used in the treatment of nr-axSpA after at least a 4-week duration of therapy **AND** an intolerance or hypersensitivity to **ONE** additional NSAID used in the treatment of nr-axSpA **OR** b. The member has an intolerance or hypersensitivity to **TWO** different NSAIDs used in the treatment of nr-axSpA **OR** c. The member has an FDA labeled contraindication to **ALL** NSAIDs used in the treatment of nr-axSpA **OR** d. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in

	DrugDex with 1 or 2a level of evidence or AHFS for the treatment of nr-axSpA **AND** 2. **ANY** of the following: a. The member has tried and had an inadequate response to at least **ONE** TNF inhibitor for nr-axSpA after at least a 3-month duration of therapy [the preferred TNF inhibitor is Cimzia (certolizumab pegol)] **OR** b. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to a TNF inhibitor for nr-axSpA **OR** c. The member has an FDA labeled contraindication to **ALL** TNF inhibitors for nr-axSpA **OR** d. **ALL** TNF inhibitors are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication
Moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA)	**BOTH** of the following: 1. **ONE** of the following: a. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., methotrexate, leflunomide) used in the treatment of PJIA after at least a 3-month duration of therapy **OR** b. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of PJIA **OR** c. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of PJIA **OR** d. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PJIA **AND** 2. **ANY** of the following:

	a. The member has tried and had an inadequate response to at least **ONE** TNF inhibitor for PJIA after at least a 3-month duration of therapy [preferred TNF inhibitors include - Adalimumab-aaty, Adalimumab-adaz, Enbrel (etanercept), Hadlima (adalimumab-bwwd), Humira (adalimumab), and Simlandi (adalimumab-ryvk)] **OR** b. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to therapy with **ONE** TNF inhibitor for PJIA **OR** c. The member has an FDA labeled contraindication to ALL TNF inhibitors for PJIA **OR** d. **ALL** TNF inhibitors are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication
Giant cell arteritis (GCA)	**ONE** of the following: 1. The member has tried and had an inadequate response to systemic corticosteroids (e.g., prednisone, methylprednisolone) used in the treatment of GCA for at least a 7 day duration of therapy **OR** 2. The member has an intolerance or hypersensitivity to systemic corticosteroids used in the treatment of GCA **OR** 3. The member has an FDA labeled contraindication to **ALL** systemic corticosteroids **OR** 4. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of GCA
Other indications	The member has another FDA labeled indication or an indication supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a

Continuation of upadacitinib (Rinvoq) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "7"):

1. An authorization or reauthorization for upadacitinib has been previously approved by Florida Blue [Note: members not previously approved for the requested agent will require initial evaluation review]

2. Member has had clinical benefit with upadacitinib
3. If the member has a diagnosis of moderate to severe atopic dermatitis, the member will continue standard maintenance therapies (e.g., topical emollients, good skin care practices) in combination with upadacitinib
4. The prescriber is a specialist in the area of the member's diagnosis (e.g., allergist, dermatologist, or immunologist for AD, gastroenterologist for CD of UC, rheumatologist for AS, GCA, nr-axSpA, PJIA, PsA or RA); or the prescriber has consulted with a specialist in the area of the member's diagnosis
5. Member does **NOT** have any FDA labeled contraindications to upadacitinib
6. Member will **NOT** be using upadacitinib in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), and Xeljanz/Xeljanz XR (tofacitinib)]; Otezla/Otezla XR (apremilast Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
7. **ANY** of the following ("a". "b", "c", or "d"):
    a. **EITHER** of the following based on indication:
        i. Atopic dermatitis, Crohn's disease, and ulcerative colitis - the dosage of upadacitinib ER tablet does not exceed 30 mg once daily
            - QL: 15 mg tablet - 1 tablet/day
            - QL: 30 mg tablet - 1 tablet/day
        ii. Psoriatic arthritis, and polyarticular juvenile idiopathic arthritis - the dosage does not exceed the following:
            a. Upadacitinib ER tablet - 15 mg once daily
                - QL: 15 mg tablet - 1 tablet/day
            b. Upadacitinib oral solution - the following based on member weight:
                - 10 kg to less than 20 kg - 3 mg (3 mL oral solution) twice daily
                    - QL: 1 mg/mL oral solution - 180 mL/30 days
                - 20 kg to less than 30 kg - 4 mg (4 mL oral solution) twice daily
                    - QL: 1 mg/mL oral solution - 240 mL/30 days
                - 30 kg and greater - 6 mg (6 mL oral solution) twice daily
                    - QL: 1 mg/mL oral solution - 360 mL/30 days
        iii. Other indications - the dosage of upadacitinib ER tablet does not exceed 15 mg once daily
            - QL: 15 mg tablet - 1 tablet/day
    b. The member has an FDA labeled indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):
        i. The requested quantity (dose) does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit

ii. **ALL** of the following ("1", "2", and "3"):

1. The requested quantity (dose) exceeds the FDA maximum labeled dose for the requested indication
2. The member has tried and had an inadequate response to at least a 3-month trial of the maximum FDA labeled dose for the requested indication (medical records required)
3. **EITHER** of the following ("a" or "b"):

a. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit

b. The requested quantity (dose) exceeds the maximum FDA labeled dose **AND** the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

c. The member has a compendia supported indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):

i. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit

ii. The requested quantity (dose) exceeds the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

d. The member does **NOT** have an FDA labeled indication **NOR** a compendia supported indication for the requested agent, **AND BOTH** of the following ("i" and "ii"):

i. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit

ii. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitation of Use (per product labeling): Upadacitinib is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with potent immunosuppressants such as azathioprine and cyclosporine.
- The recommended dose 15 mg once daily

- Treatment of adults and pediatric patients 2 years of age and older with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.
  - Limitation of Use (per product labeling): Use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.
  - The recommended dosage is based on age and body weight:
    - Pediatric patients 2 to less than 18 years of age:
      - 10 kg to less than 20 kg – 3 mg (3 mL oral solution) twice daily
      - 20 kg to less than 30 kg – 4 mg (4 mL oral solution) twice daily
      - 30 kg and greater – 6 mg (6 mL oral solution) twice daily or 15 mg (one 15 mg tablet) once daily
    - Adults 18 years of age and older:
      - 15 mg once daily
- Treatment of adults and pediatric patients 12 years of age and older 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.
  - Limitations of Use (per product labeling): Upadacitinib is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.
  - The recommended dose is as follows:
    - Pediatric Patients 12 Years of Age and Older Weighing at Least 40 kg and Adults Less Than 65 Years of Age - Initiate treatment with 15 mg once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg once daily. Discontinue if an adequate response is not achieved with the 30 mg dose. Use the lowest effective dose needed to maintain response.
    - Adults 65 Years of Age and Older - 15 mg once daily.
- Treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response or intolerance to one or more TNF blockers. If TNF blockers are clinically inadvisable, patients should have received at least one approved systemic therapy prior to use of upadacitinib.
  - Limitations of Use (per product labeling): Upadacitinib is not recommended for use in combination with other JAK inhibitors, biological therapies for ulcerative colitis, or with potent immunosuppressants such as azathioprine and cyclosporine.
  - The recommended induction dose is 45 mg once daily for 8 weeks.
  - The recommended dose for maintenance treatment is 15 mg once daily. A dosage of 30 mg once daily may be considered for patients with refractory, severe or extensive disease. Discontinue if an adequate therapeutic response is not achieved with the 30 mg dosage. Use the lowest effective dosage needed to maintain response.
- Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to one or more TNF blockers. If TNF blockers are clinically

inadvisable, patients should have received at least one approved systemic therapy prior to use of upadacitinib.

  - Limitations of Use (per product labeling): Upadacitinib is not recommended for use in combination with other JAK inhibitors, biological therapies for Crohn's disease, or with potent immunosuppressants such as azathioprine and cyclosporine.
  - The recommended induction dose is 45 mg once daily for 12 weeks.
  - The recommended dose for maintenance treatment is 15 mg once daily. A dosage of 30 mg once daily may be considered for patients with refractory, severe or extensive disease. Discontinue if an adequate therapeutic response is not achieved with the 30 mg dosage. Use the lowest effective dosage needed to maintain response.

- Treatment of adults with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers.
  - Limitation of Use (per product labeling): Use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.
  - The recommended dose is 15 mg once daily
- Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy.
  - Limitation of Use (per product labeling): Use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.
  - The recommended dose is 15 mg once daily
- Treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.
  - Upadacitinib is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with potent immunosuppressants such as azathioprine and cyclosporine
  - The recommended dosage is based on body weight:
    - 10 kg to less than 20 kg – 3 mg (3 mL oral solution) twice daily
    - 20 kg to less than 30 kg – 4 mg (4 mL oral solution) twice daily
    - 30 kg and greater – 6 mg (6 mL oral solution) twice daily or 15 mg (one 15 mg tablet) once daily
- Treatment of adults with giant cell arteritis (GCA).
  - Limitation of Use (per product labeling): Upadacitinib is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.
  - The recommended dosage is 15 mg once daily in combination with a tapering course of corticosteroids. 15 mg once daily can be used as monotherapy following discontinuation of corticosteroids.

Dose Adjustments

- Renal Impairment - No dose adjustment is required in patients with mild, moderate or severe renal impairment for the treatment of AS, GCA, nr-axSpA, RA, PJIA, or PsA. However, for patients with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2) and treatment of atopic dermatitis, the

maximum recommended dosage is 15 mg once daily. For patients with severe renal impairment and treatment of CD or UC, the maximum recommended induction dose is 30 mg once daily for 12 weeks (CD) or 8 weeks (UC) followed by a maintenance dose of 15 mg once daily. Use has not been studied in subjects with end stage renal disease (eGFR <15 mL/min/1.73 m^2), and therefore not recommended for use in this population.

- Hepatic Impairment - No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment for AS, GCA, nr-axSpA, RA, PJIA, PsA, and atopic dermatitis. For patients with mild or moderate hepatic impairment and treatment of CD or UC, the maximum recommended induction dose is 30 mg once daily for 12 weeks (CD) or 8 weeks (UC) followed by a maintenance dose of 15 mg once daily. Use has not been studied in patients with severe hepatic impairment (Child Pugh C), and therefore not recommended for use in this population.
- Drug Interactions
    - CYP3A4 inhibitors - Exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole and clarithromycin). No dosage adjustment is needed in patients receiving strong CYP3A4 inhibitors and treated for AS, GCA, nr-axSpA, RA, PJIA, or PsA. For patients with atopic dermatitis taking strong CYP3A4 inhibitors, reduce the upadacitinib dose to 15 mg once daily. For patients with CD or UC taking strong CYP3A4 inhibitors, reduce the upadacitinib induction dosage to 30 mg once daily. The recommended maintenance dosage is 15 mg once daily.
    - CYP3A4 inducers - Exposure is decreased when co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect. Coadministration of upadacitinib with strong CYP3A4 inducers is not recommended.
- Adverse Effects
    - Serious infection - interrupt treatment until the infection is controlled
    - Absolute Neutrophil Count (ANC) <1,000 cells/mm^3 - interrupt therapy until ALC ≥1,000 cells/mm^3
    - Absolute Lymphocyte Count (ALC) <500 cells/mm^3 - interrupt therapy until ALC ≥500 cells/mm^3
    - Hg <8 g/dL - interrupt therapy until Hg ≥8 g/dL
    - Hepatic transaminases - interrupt therapy if drug-induced liver injury is suspected

Drug Availability

- Rinvoq
    - 15 mg and 30 mg extended-release tablets in 30-count bottles
    - 45 mg extended-release tablets in 28-count bottles
    - Store at 2˚C to 25˚C (36˚F to 77˚F). Store in the original bottle in order to protect from moisture.
- Rinvoq LQ
    - 1 mg/mL oral solution in HDPE bottles with a child-resistant cap. Each bottle contains a labeled volume of 180 mL of clear, colorless to light yellow solution. The bottle is packaged in a carton with one press-in bottle adapter and one 10 mL oral dosing syringe.
    - Store between 2°C to 30°C (36°F to 86°F). Discard remaining oral solution 60 days after opening the bottle.

PRECAUTIONS:

Boxed Warning

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

- SERIOUS INFECTIONS
    - Patients treated with Rinvoq/Rinvoq LQ are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.
    - If a serious infection develops, interrupt Rinvoq/Rinvoq LQ until the infection is controlled.
    - Reported infections include:
        - Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Rinvoq/Rinvoq LQ use and during therapy. Treatment for latent infection should be considered prior to Rinvoq/Rinvoq LQ use.
        - Invasive fungal infections, including cryptococcosis and pneumocystosis.
        - Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.
    - The risks and benefits of treatment with Rinvoq/Rinvoq LQ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.
    - Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Rinvoq/Rinvoq LQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.
- MORTALITY
    - In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor.
- MALIGNANCIES
    - Lymphoma and other malignancies have been observed in patients treated with Rinvoq. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk.
- MAJOR ADVERSE CARDIOVASCULAR EVENTS
    - In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue Rinvoq/Rinvoq LQ in patients that have experienced a myocardial infarction or stroke.
- THROMBOSIS
    - Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated for inflammatory conditions with JAK inhibitors, including Rinvoq. Many of these adverse events were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid

Rinvoq/Rinvoq LQ in patients at risk. Patients with symptoms of thrombosis should discontinue Rinvoq/Rinvoq LQ and be promptly evaluated.

Contraindications

- Patients with known hypersensitivity to upadacitinib or any of the excipients in Rinvoq/Rinvoq LQ

Precautions/Warnings

- **Serious Infections** – see Boxed Warning
- **Mortality** – see Boxed Warning
- **Malignancy and Lymphoproliferative Disorders** – see Boxed Warning
- **Major Adverse Cardiovascular Events** – See Boxed Warning
- **Thrombosis** – see Boxed Warning
- **Hypersensitivity Reactions** - Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving upadacitinib in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue upadacitinib and institute appropriate therapy
- **Gastrointestinal (GI) Perforations** - Gastrointestinal perforations have been reported in clinical trials with upadacitinib. Monitor patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis and those taking concomitant medications including NSAIDs or corticosteroids). Evaluate promptly patients presenting with new onset abdominal pain for early identification of gastrointestinal perforation.
- **Laboratory Parameters**
    - **Neutropenia** - Treatment with upadacitinib was associated with an increased incidence of neutropenia. Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt upadacitinib treatment in patients with a low neutrophil count (i.e., ANC less than 1.000 cells/mm^3).
    - **Lymphopenia** - ALC less than 500 cells/mm^3 were reported in upadacitinib clinical studies. Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt upadacitinib treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3).
    - **Anemia** - Decreases in hemoglobin levels to less than 8 g/dL were reported in upadacitinib clinical studies. Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt upadacitinib treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL).
    - **Lipids** - Treatment with upadacitinib was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Patients should be monitored 12 weeks after initiation of treatment, and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia.
    - **Liver Enzyme Elevations** - Treatment with upadacitinib was associated with increased incidence of liver enzyme elevation compared to placebo. Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, upadacitinib should be interrupted until this diagnosis is excluded.

- **Embryo-Fetal Toxicity** - Based on findings in animal studies, upadacitinib may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Advise pregnant women of the potential risk to a fetus. Verify the pregnancy status of patients of reproductive potential prior to starting treatment. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with upadacitinib and for 4 weeks following completion of therapy.
- **Vaccination** - Use of live, attenuated vaccines during, or immediately prior to, upadacitinib therapy is not recommended. Prior to initiating upadacitinib, it is recommended that patients be brought up to date with all immunizations, including prophylactic zoster vaccinations, in agreement with current immunization guidelines.
- **Medication Residue in Stool** - Reports of medication residue in stool or ostomy output have occurred in patients taking upadacitinib. Most reports described anatomic (e.g., ileostomy, colostomy, intestinal resection) or functional gastrointestinal conditions with shortened gastrointestinal transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly. Monitor patients clinically and consider alternative treatment if there is an inadequate therapeutic response.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

K50.00 – K50.919	Crohn’s disease [regional enteritis]
K51.00 – K51.919	Ulcerative colitis
L40.50 – L40.59	Arthropathic psoriasis
L20.0	Besnier's prurigo
L20.81	Atopic neurodermatitis
L20.82	Flexural eczema
L20.84	Intrinsic (allergic) eczema
L20.89	Other atopic dermatitis
L20.9	Atopic dermatitis, unspecified
M05.00 – M05.09	Felty's syndrome
M05.10 – M05.19	Rheumatoid lung disease with rheumatoid arthritis
M05.20 – M05.29	Rheumatoid vasculitis with rheumatoid arthritis
M05.30 – M05.39	Rheumatoid heart disease with rheumatoid arthritis
M05.40 – M05.49	Rheumatoid myopathy with rheumatoid arthritis
M05.50 – M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis
M05.60 – M05.69	Rheumatoid arthritis with involvement of other organs and systems
M05.70 – M05.7A	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80 – M05.8A	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified

M05.A	Abnormal rheumatoid factor and anti-citrullinated protein antibody with rheumatoid arthritis
M06.00 – M06.0A	Rheumatoid arthritis without rheumatoid factor
M06.20 – M06.29	Rheumatoid bursitis
M06.30 – M06.39	Rheumatoid nodule
M06.80 – M06.8A	Other specified rheumatoid arthritis
M06.9	Rheumatoid arthritis, unspecified
M08.09	Unspecified juvenile rheumatoid arthritis, multiple sites
M08.3	Juvenile rheumatoid polyarthritis (seronegative)
M08.89	Other juvenile arthritis, multiple sites
M31.5	Giant cell arteritis with polymyalgia rheumatica
M31.6	Other giant cell arteritis
M45.0 – M45.9	Ankylosing spondylitis
M45.A0 – M45.AB	Non-radiographic axial spondyloarthritis
M46.81 – M46.89	Other specified inflammatory spondylopathies

REIMBURSEMENT INFORMATION:

Refer to section entitled.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Crohn's disease: A chronic granulomatous inflammatory disease of unknown etiology, involving any part of the gastrointestinal tract from mouth to anus, but commonly involving the terminal ileum with scarring and thickening of the bowel wall.

DMARDs: An acronym for disease-modifying antirheumatic drugs. These are drugs that modify the rheumatic disease processes, and slow or inhibit structural damage to cartilage and bone. These drugs are unlike symptomatic treatments such as NSAIDs that do not alter disease progression. DMARDs can be further subcategorized. With the release of biologic agents (e.g., anti-TNF drugs), DMARDs were divided into either: (1) conventional, traditional, synthetic, or non-biological DMARDs; or as (2)

biological DMARDs. However, with the release of newer targeted non-biologic drugs and biosimilars, DMARDs are now best categorized as: (1) conventional synthetic DMARDs (csDMARD) (e.g., MTX, sulfasalazine), (2) targeted synthetic DMARDs (tsDMARD) (e.g., baricitinib, tofacitinib, apremilast), and (3) biological DMARDs (bDMARD), which can be either a biosimilar DMARD (bsDMARD) or biological originator DMARD

Eczema Area Severity Index score (EASI) - assesses severity (severity score) and body surface area affected by erythema, induration/papulation/edema, excoriations, and lichenification (area score), which are graded systematically for each of 4 anatomical regions (head and neck, trunk, upper limbs, lower limbs) and assembled in a composite score, with a score range of 0 to 72.

- EASI 50 - a percentage improvement of EASI score from baseline that is ≥50%
- EASI 75 - a percentage improvement of EASI score from baseline that is ≥75%
- EASI 90 - a percentage improvement of EASI score from baseline that is ≥90%

Helper T cells (a.k.a., CD4+ T cells) – a type of lymphocyte or white blood cell (WBC) that matures in the thymus and play an important role in cell-mediated immunity. T helper cells assist other WBCs in immunologic processes by releasing T cell cytokines. Different types of T helper cells secrete different cytokines (e.g., type 2 release IL-4, IL-5, IL-9, IL-10 and IL-13)

Intertriginous area – an area where two skin areas may touch or rub together (e.g., axilla of the arm, the anogenital region, skin folds of the breasts, between digits)

Lichenified - skin that has become thickened and leathery. This often results from continuously rubbing or scratching the skin.

Moderate to Severe Crohn's Disease: Moderate to severe disease applies to patients who have failed to respond to treatment for mild to moderate disease or those with more prominent symptoms of fevers, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.

Patient-Oriented Eczema Measure (POEM) – a validated questionnaire, examining seven items (scored 0 to 4 based on frequency of event), used in clinical settings to assess time spent with symptoms and the impact of symptoms on sleep, with a score range of 0 to 28.

Pruritus – itching

Psoriatic arthritis (PsA): joint inflammation that occurs in about 5% to 10% of people with psoriasis (a common skin disorder). It is a severe form of arthritis accompanied by inflammation, psoriasis of the skin or nails, and a negative test for rheumatoid factor. Enthesitis refers to inflammation of entheses, the site where ligaments or tendons insert into the bones. It is a distinctive feature of PsA and does not occur with other forms of arthritis. Common locations for enthesitis include the bottoms of the feet, the Achilles' tendons, and the places where ligaments attach to the ribs, spine, and pelvis.

Rheumatoid arthritis: usually occurs between ages 20 and 50. Inflammation begins in a joint, usually those of the fingers and hands, resulting in pain, swelling, redness, and eventually joint deformity. It is considered an autoimmune disease, which can affect the entire body, causing fatigue, weight loss, weakness, fever, and loss of appetite. It affects each person differently, with symptoms ranging from

mild to debilitating. In many cases, it is difficult to control. In about one in six cases, rheumatoid arthritis becomes severely debilitating and can shorten the life of the person affected.

Scoring Atopic Dermatitis (SCORAD) - the extent and severity of AD over the body area and the severity of 6 specific symptoms (erythema, edema/papulation, excoriations, lichenification, oozing/crusts, and dryness) are assessed and scored by the investigator. Subjective assessment of itch and sleeplessness is scored by the patient. The SCORAD score is a combined score of body area affected, and investigator and patient symptom scoring, with a score range of 0 to103.

RELATED GUIDELINES:

Abatacept (Orencia), 09-J0000-67
Adalimumab Products, 09-J0000-46
Anakinra (Kineret), 09-J0000-45
Baricitinib (Olumiant), 09-J3000-10
Certolizumab Pegol (Cimzia), 09-J0000-77
Dupilumab (Dupixent), 09-J2000-80
Etanercept (Enbrel), 09-J0000-38
Golimumab (Simponi, Simponi Aria), 09-J1000-11
Guselkumab (Tremfya), 09-J2000-87
Infliximab Products, 09-J0000-39
Ixekizumab (Taltz), 09-J2000-62
Mirikizumab (Omvoh), 09-J4000-71
Psoralens with Ultraviolet A (PUVA), 02-10000-16
Rituximab (Rituxan), 09-J0000-59
Risankizumab (Skyrizi), 09-J3000-45
Sarilumab (Kevzara), 09-J2000-88
Secukinumab (Cosentyx), 09-J2000-30
Tocilizumab Products (Actemra, Tofidence, Tyenne), 09-J1000-21
Tofacitinib (Xeljanz, Xeljanz XR) Oral Solution, Tablet and Extended-Release Tablet, 09-J1000-86
Ustekinumab (Stelara), 09-J1000-16
Vedolizumab (Entyvio), 09-J2000-18

OTHER:

NOTE: The list of biologic immunomodulator agents not permitted as concomitant therapy can be found at Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.

Table 2: Conventional Synthetic DMARDs

Generic Name	Brand Name
Auranofin (oral gold)	Ridaura
Azathioprine	Imuran
Cyclosporine	Neoral, Sandimmune
Hydroxychloroquine	Plaquenil
Leflunomide	Arava

Methotrexate	Rheumatrex, Trexall
Sulfasalazine	Azulfidine, Azulfidine EN-Tabs

Table 3: Grading of Severity of Rheumatoid Arthritis

Severity	Criteria
Mild	Joint pain Inflammation of at least 3 joints No inflammation in tissues other than the joints Usually, a negative result on a rheumatoid factor test An elevated erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) level No evidence of bone or cartilage damage on x-rays
Moderate	Between 6 and 20 inflamed joints Usually no inflammation in tissues other than the joints An elevated ESR or CRP levels A positive rheumatoid factor test or anti-cyclic citrullinated peptide (anti-CCP) antibodies Evidence of inflammation but no evidence of bone damage on x-rays
Severe	More than 20 persistently inflamed joints or a rapid loss of functional abilities Elevated ESR or CRP levels Anemia related to chronic illness Low blood albumin level A positive rheumatoid factor test, often with a high level Evidence of bone and cartilage damage on x-ray Inflammation in tissues other than joints

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/12/25.

GUIDELINE UPDATE INFORMATION:

01/01/20	New Medical Coverage Guideline.
07/01/20	Revision to guideline consisting of updating the description and position statement.
01/01/21	Review and revision to guideline consisting of updating the position statement and references.

03/15/21	Revision to guideline consisting of updating Table 1 in the position statement.
09/15/21	Update to Table 1 in Position Statement.
11/15/21	Revision to guideline consisting of updating the position statement.
01/01/22	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, other section, and references.
02/15/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, related guidelines, and references.
03/15/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, related guidelines, and references.
05/15/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, billing/coding, and references.
07/15/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, billing/coding, and references.
09/15/22	Revision to guideline consisting of updating the position statement.
01/01/23	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, billing/coding, and references based on the new FDA-approved indication of active non-radiographic axial spondyloarthritis.
04/15/23	Update to Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.
07/01/23	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, definitions, related guidelines, other section, and references. Crohn's disease added as a new covered indication per FDA approval. Rinvoq is a Step 1b agent for CD. Amjevita and Hadlima added as Step 1a agents. Humira biosimilar products added to list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
01/01/24	Review and revision to guideline consisting of updating the description (atopic dermatitis info), position statement, other section, and references. Added additional parameters for diagnosis of "moderate-to-severe" atopic dermatitis. Amjevita low-concentration [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] clarified as the preferred prerequisite product. Update to Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.
05/15/24	Revision to guideline consisting of updating the description section, position statement, and references. Removal of the step requirement of a systemic immunosuppressant for AD (based on new AD guidelines).
07/01/24	Revision to guideline consisting of updating the description section, position statement, dosage/administration, related guidelines, billing/coding, definitions, other section, and references. New FDA-approved indication for PJIA and age expanded to 2 years and older for psoriatic arthritis. New liquid formulation, Rinvoq LQ, approved for use. Amjevita low-concentration removed as a required prerequisite agent. Updates to the positioning of agents in Table 1. Removal of latent TB testing requirement. New drugs added to the list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
10/01/24	Revision to guideline consisting of updating the position statement. Updates to Table 1. Simlandi added among the required prerequisite agents for AS, PJIA, PsA, RA, CD, and UC.

01/01/25	Review and revision to guideline consisting of updating the description, position statement, other section, and references. Adalimumab-aaty and Adalimumab-adaz added among the preferred adalimumab products. Revised wording regarding maximum dosage exceptions. Update to original Table 1 which is now a link out from the Position Statement. Table titles updated. New drugs were added to the list of drugs that are not permitted for use in combination.
07/01/25	Revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding, and references. New FDA-approved indication for GCA in adults. Rinvoq is a Step 1a agent for GCA.
10/01/25	Revision: Added ICD-10 code M05.A. Updated ICD-10 code ranges for RA.
01/01/26	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, and references. Rinvoq moved from a Step 1b agent to a Step 2 agents for CD and UC.