09-J3000-51

Original Effective Date: 01/01/20

Reviewed: 11/08/23

Revised: 01/01/24

Subject: Upadacitinib (Rinvoq™) Tablets

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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.

RHEUMATOID DISORDERS

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is the most common inflammatory autoimmune arthritis in adults. The main goal of therapy is to achieve remission, but additional goals include decrease inflammation, relieve symptoms, prevent joint and organ damage, improve physical function/overall well-being, and reduce long term complications. 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 DMARD(s) chosen
- Recommendations are limited to DMARDs approved by the US FDA for treatment of RA:
    - csDMARDs: hydroxychloroquine, sulfasalazine, methotrexate (MTX), leflunomide
    - bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab)
    - tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
- Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide
- Biosimilars are considered equivalent to FDA-approved originator bDMARDs
- 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

- 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 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

Early use of DMARD, particularly MTX, is recommended as soon as possible following diagnosis of RA. Dosing of MTX for RA is once weekly dosing with starting doses at 7.5 mg or 15 mg once weekly. MTX dose is increased as tolerated and as needed to control symptoms and signs of RA disease. The usual target dose is at least 15 mg weekly, and the usual maximum dose is 25 mg weekly. ACR defines optimal dosing for RA treatments as 1) dosing to achieve a therapeutic target derived from mutual patient-clinician consideration of patient priorities and 2) given for at least 3 months before therapy escalation or switching. For patients who are unable to take MTX, hydroxychloroquine, sulfasalazine, or leflunomide are other DMARD options. In patients resistant to initial MTX treatment, combination DMARD (e.g., MTX plus sulfasalazine or hydroxychloroquine or a TNF-inhibitor) is recommended.

For patients who are resistant to MTX after 3 months of treatment at optimal doses (usually 25 mg per week), it is recommended to either use DMARD triple therapy with MTX plus sulfasalazine and hydroxychloroquine or combination of MTX with TNF inhibitor. Triple therapy regimen has been found to be of similar clinical efficacy to MTX with biologics in several randomized trials, including in patients with high level of disease activity or with adverse prognostic features. The use of triple therapy has been shown to be highly cost-effective compared with combining a biologic with MTX, providing comparable or near comparable clinical benefit. The use of biologic with MTX combination is preferred when

patients have high disease activity and clinical benefit from a more rapid response is needed and when patients who do not achieve satisfactory response within 3 months with non-biologic triple therapy following an inadequate response to MTX therapy.

Psoriatic Arthritis (PsA)

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, most commonly presenting with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Treatment involves the use of a variety of interventions, including many agents used for the treatment of other inflammatory arthritis, particularly spondyloarthritis and RA, and other management strategies of the cutaneous manifestations of psoriasis.

The American Academy of Dermatology (AAD) recommends initiating MTX in most patients with moderate to severe PsA. After 12 to 16 weeks of MTX therapy with appropriate dose escalation, the AAD recommends adding or switching to a TNF inhibitor if there is minimal improvement on MTX monotherapy.

The American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) guidelines for PsA recommend a treat-to-target approach in therapy, regardless of disease activity, and the following:

- Active PsA is defined as symptoms at an unacceptably bothersome level as reported by the patient and health care provider to be due to PsA based on the presence of one of the following:
    - Actively inflamed joints
    - Dactylitis
    - Enthesitis
    - Axial disease
    - Active skin and/or nail involvement
    - Extraarticular manifestations such as uveitis or inflammatory bowel disease
- Disease severity includes level of disease activity at a given time point and the presence/absence of poor prognostic factors and long-term damage
- Severe PsA disease includes the presence of 1 or more of the following:
    - Erosive disease
    - Elevated markers of inflammation (ESR, CRP) attributable to PsA
    - Long-term damage that interferes with function (i.e., joint deformities)
    - Highly active disease that causes a major impairment in quality of life
    - Active PsA at many sites including dactylitis, enthesitis
    - Function limiting PsA at a few sites
    - Rapidly progressive disease
- Symptomatic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, local glucocorticoid injections
- Treatment recommendations for active disease:

- Treatment naïve patients first line options include oral small molecules (OSM), TNF biologics, IL-17 inhibitor, and IL-12/23 inhibitor
    - OSM (i.e., methotrexate [MTX], sulfasalazine, cyclosporine, leflunomide, apremilast) should be considered if the patient does not have severe PsA, does not have severe psoriasis, prefers oral therapy, has concern over starting a biologic, or has contraindications to TNF inhibitor
    - Biologics (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) are recommended as a first line option in patients with severe PsA and/or severe psoriasis
- Previous treatment with OSM and continued active disease:
    - Switch to a different OSM (except apremilast) in patients without severe PsA or severe PS, contraindications to TNF biologics, prefers oral therapy OR add on apremilast to current OSM therapy
    - May add another OSM (except apremilast) to current OSM therapy for patients that have exhibited partial response to current OSM in patients without severe PsA or severe PS, contraindications to TNF biologics, or prefers oral therapy
    - Biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) monotherapy
- Previous treatment with a biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) and continued active disease:
    - Switch to another biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, or tofacitinib) monotherapy or add MTX to the current TNF biologic

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, with the additional use of disease-modifying antirheumatic drugs (DMARDs) in patients with peripheral arthritis. The American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) recommend the following pharmacological treatment for AS:

- Stable AS: First line therapy with on demand NSAIDs; there is also a conditional recommendation for continuation of TNF inhibitor as monotherapy
- Active AS:
    - First line therapy with continuous NSAIDs with physical therapy
    - TNF inhibitor recommended for patients with active AS despite an adequate trial with NSAIDs
        - Lack of response (or intolerance) to at least 2 different NSAIDs over 1 month or incomplete response to at least 2 different NSAIDs over 2 months would be an adequate NSAID trial to judge response
    - Recommendations for nonresponse to TNF therapy (all conditional):

        - Primary nonresponse: switch to secukinumab or ixekizumab over another TNF
        - Secondary nonresponse: switch to another TNF over a non-TNF biologic
        - Recommend against addition of sulfasalazine or MTX
        - Recommend against switching to a biosimilar of the failed TNF
    - TNF-inhibitors are conditionally recommended over secukinumab or ixekizumab
    - Secukinumab or ixekizumab are conditionally recommended over DMARDs in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
    - DMARDs (i.e., methotrexate [MTX], sulfasalazine) are only conditionally recommended in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
    - Methotrexate is not recommended as add on therapy to TNF inhibitors in stable and active AS
    - If patient has concomitant inflammatory bowel disease (IBD) or recurrent uveitis, TNF-inhibitors are recommended over other biologics
    - Glucocorticoids are not recommended

Nonradiographic Axial Spondyloarthritis (nr-axSpA)

Nonradiographic axial spondyloarthritis (nr-axSpA) falls under the same spondyloarthritis family as ankylosing spondylitis (AS). Nr-axSpA includes patients with chronic back pain and features suggestive of spondyloarthritis (SpA), but do not meet the classification of AS. The goals of treatment 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 NSAIDs and exercise, with the additional use of DMARDs in patients with peripheral arthritis. The American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) recommendation for nr-axSpA are the same as AS:

- Stable SpA: conditional recommendation for on-demand treatment with NSAIDs
- Active SpA:
    - First line therapy with continuous NSAIDs with physical therapy
    - TNF inhibitor conditionally recommended for patients with active SpA despite an adequate trial with NSAIDs
        - Lack of response (or intolerance) to at least 2 different NSAIDs over 1 month or incomplete response to at least 2 different NSAIDs over 2 months would be an adequate NSAID trial to judge response
    - TNF-inhibitors are conditionally recommended over secukinumab or ixekizumab
    - Secukinumab or ixekizumab are conditionally recommended over DMARDs in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
    - Recommendations for nonresponse to TNF therapy (all conditional):
        - Primary nonresponse: switch to secukinumab or ixekizumab over another TNF
        - Secondary nonresponse: switch to another TNF over a non-TNF biologic
        - Recommend against addition of sulfasalazine or MTX

        - Recommend against switching to a biosimilar of the failed TNF
    - DMARDs (i.e., methotrexate, sulfasalazine) are only conditionally recommended in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
    - Methotrexate is not recommended as add on therapy to TNF inhibitors in stable and active AS
    - If patient has concomitant inflammatory bowel disease or recurrent uveitis, TNF-inhibitors are recommended over other biologics
    - Glucocorticoids are not recommended

INFLAMMATORY BOWEL DISEASE

Crohn's Disease (CD)

Crohn's Disease (CD) is an inflammatory condition that can affect any portion of the gastrointestinal tract from the mouth to the perianal area. Choice of therapy is dependent on the anatomic location of disease, the severity of disease, and whether the treatment goal is to induce remission or maintain remission. The American Gastroenterological Association (AGA) 2021 guideline recommends the following:

- 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
    - Anti-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)
- DMARD therapy:
    - Corticosteroids are suggested over no treatment for the induction of remission, and are recommended against for maintenance of remission
    - 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 2018 American College of Gastroenterology (ACG) guidelines recommend the following:

- Mild to moderately severe disease/low risk disease:
  - Sulfasalazine (in doses of 3-6 grams daily) is effective in colonic and/or ileocolonic CD, but not those with isolated small bowel disease
  - 5-aminosalicylic (ASA) suppositories and enema preparations are effective for induction and maintenance of remission in rectal and sigmoid disease
  - Conventional corticosteroids are primarily used for the treatment of flares, and are often used as a bridge until immunomodulators and/or biologic agents become effective
  - Controlled ileal release budesonide is effective for induction of remission in ileocecal disease
- Moderate to severe disease/moderate to high risk disease
  - Corticosteroids are effective for short-term use in alleviating signs and symptoms of moderate to severely active CD, but do not induce mucosal healing and should be used sparingly
  - Azathioprine, 6-mercaptopurine, or MTX (15 mg once weekly) may be used in treatment of active disease and as adjunctive therapy for reducing immunogenicity against biologic therapy
  - TNF inhibitors should be used to treat CD that is resistant to treatment with corticosteroids and that is refractory to thiopurines or MTX
  - Vedolizumab with or without an immunomodulator should be considered for induction of symptomatic remission for patients with moderate to severely active CD and objective evidence of active disease

- Ustekinumab should be used in patients that have failed previous treatment with corticosteroids, thiopurines, MTX, or TNF inhibitors, or in patients with no prior TNF inhibitor exposure

- Severe/fulminant disease:
  - IV corticosteroids should be used
  - TNF inhibitors can be considered
- Maintenance therapy:
  - Thiopurines or methotrexate should be considered once remission is induced with corticosteroids
  - TNF inhibitors, specifically infliximab, adalimumab, and certolizumab pegol, should be used in combination with azathioprine, MTX, or 6-mercaptopurine to maintain remission of TNF induced remission
  - Vedolizumab should be used for maintenance of remission of vedolizumab induced remission
  - Ustekinumab should be used for maintenance of remission of ustekinumab induced remission

Ulcerative Colitis (UC)

Ulcerative colitis (UC) is a chronic immune-mediated inflammatory condition affecting the large intestine associated with inflammation of the rectum, but that can extend to involve additional areas of the colon. The American College of Gastroenterology (ACG) recommends a treat-to-target approach and recommend therapeutic management should be guided by diagnosis (i.e., Montreal classification), assessment of disease activity (i.e., mild, moderate, and severe), and disease prognosis. The ACG treatment recommendations are further broken down into induction therapies and maintenance of remission. The 2019 ACG treatment guidelines recommend the following for therapeutic management of UC:

Induction of remission:

- Mildly active disease:
  - Rectal 5-ASA at a dose of 1 g/day with or without oral 5-ASA at a dose of at least 2 g/day for left-sided UC
  - Rectal 5-ASA at a dose of 1 g/day for ulcerative proctitis
  - Oral 5-ASA at a dose of at least 2 g/day for extensive UC
  - Add oral budesonide multi-matrix (MMX) 9 mg/day for patients that are intolerant or non-responsive to oral and/or rectal and oral 5-ASA at appropriate doses
- Moderately active disease:
  - Oral budesonide multi-matrix (MMX) 9 mg/day for induction of remission
- Moderately to severely active disease:
  - Oral systemic corticosteroids, TNF inhibitors (i.e., adalimumab, golimumab, or infliximab), tofacitinib, or vedolizumab to induce remission
  - Combination of infliximab with thiopurine therapy when using infliximab for induction

- Switch to tofacitinib or vedolizumab for induction in patients that have failed TNF inhibitors
- Patients with initial response to TNF inhibitors that lose response should have antibody levels and serum drug levels tested to assess reason for loss of response. If serum levels are adequate, use of another TNF inhibitor is not likely to be of benefit.

Maintenance of remission:

- Previously mildly active disease:
  - Rectal 5-ASA at a dose of 1 g/day in patients with ulcerative proctitis
  - Oral 5-ASA at a dose of at least 2 g/day in patients with left-sided or extensive UC
- Previously moderately to severely active disease:
  - Thiopurines in patients that achieved remission due to corticosteroid induction
  - Continue TNF inhibitors (i.e., adalimumab, golimumab, or infliximab) for remission due to TNF induction
  - Continue vedolizumab for remission due to vedolizumab induction
  - Continue tofacitinib for remission due to tofacitinib induction

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

- Use either standard-dose mesalamine (2-3 g/day) or diazo-bonded 5-ASA for patients with extensive UC for induction of remission and maintenance of remission
- May add rectal mesalamine to oral 5-ASA in patients with extensive or left-sided UC for induction of remission and maintenance of remission
- Use high dose mesalamine (>3 g/day) with rectal mesalamine in patients with suboptimal response to standard-dose mesalamine, diazo-bonded 5-ASA, or with moderate disease activity 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

The American Gastroenterology Association (AGA) published recommendations for the management of moderate to severe UC.

- Standard of care is to continue agents initiated for induction therapy as maintenance therapy, if they are effective (excluding corticosteroids and cyclosporine)
- Adult outpatients with moderate to severe UC:
  - Infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab are strongly recommended over no treatment
  - Biologic naïve patients:
    - infliximab or vedolizumab are conditionally recommended over adalimumab for induction of remission
    - Recommend tofacitinib only be used in the setting of a clinical or registry study

- Previous exposure to infliximab, particularly those with primary non-response, ustekinumab or tofacitinib are conditionally recommended over vedolizumab or adalimumab for induction of remission
- Conditionally recommend against use of thiopurine monotherapy for induction, but may be used for maintenance of remission over no treatment

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 1 to 5% 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.60 Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with nonpharmacological interventions (e.g., emollient use), conventional topical therapies (including corticosteroids and calcineurin inhibitors) and environmental and occupational modifications, when necessary. The American Academy of Dermatology (AAD) guidelines suggest application of moisturizers should be an integral part of the treatment of patients with AD as there is strong evidence that their use reduces disease severity and need for pharmacologic intervention. They are an important component of maintenance treatment and prevention of flares. The AAD recommends topical corticosteroids (TCS) for patients who fail to respond to good skin care and regular use of emollients alone. Proactive, intermittent use of topical corticosteroids as maintenance therapy (1 to 2 times weekly) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone. Monitoring by physical exam for cutaneous side effects during long-term, potent steroid use is suggested. Proactive, once to twice weekly application of mid-potency TCS for up to 40 weeks has not demonstrated adverse events (e.g., purpura, telangiectasia, striae, focal hypertrichosis, acneiform/rosacea-like eruptions, skin atrophy) in clinical trials. It is recommended that patients with acute flares use super high or high potency topical corticosteroids for one to two weeks, and then replace these with lower potency preparations until the lesions resolve. AAD notes that mid- to higher potency topical corticosteroids are appropriate for short courses to gain rapid control of symptoms, but long-term management should use the least-potent corticosteroid that is effective. In general, if AD is not responding after 2 weeks of treatment, evaluation to determine other treatment plans is indicated.

Topical calcineurin inhibitors (TCIs) (e.g., pimecrolimus, tacrolimus) are recommended by the AAD as second-line therapy and are effective for acute and chronic treatment. They are particularly useful in selected clinical situations such as recalcitrance to steroids; for sensitive areas (face, anogenital, skin folds); for steroid-induced atrophy; and when there is long-term uninterrupted topical steroid use. TCIs are recommended for use on actively affected areas as a steroid-sparing agent. Proactive, intermittent use of TCIs as maintenance therapy (2 to 3 times per week) on areas that commonly flare is recommended to help prevent relapses while reducing need for topical corticosteroids and is more effective than use of emollients alone. Prescribing information for Elidel (pimecrolimus) cream and Protopic (tacrolimus) ointment indicate evaluation after 6 weeks if symptoms of AD do not improve for adults and pediatrics.

Phototherapy is recommended as a treatment for both acute and chronic AD in children and adults, after failure of the mentioned above. Systemic immunomodulator agents are indicated and recommended for the subset of adult and pediatric patients in whom optimized topical regimens using emollients, topical anti-inflammatory therapies, adjunctive methods, and/or phototherapy do not adequately control the signs and symptoms of disease. Photo therapy and systemic immunomodulating agents may also be used in patients whose medical, physical, and/or psychological states are greatly affected by their skin disease. Oral cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil are the most commonly used systemic immunomodulators and most efficacious for treating AD. The AAD recommends that systemic corticosteroids should be avoided if possible and should exclusively be reserved for acute, severe exacerbations and as a short-term bridge to other systemic, steroid sparing therapies.

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

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 self-administered products with prerequisites for certain indications are as follows:

Table 1

Disease State	Step 1		Step 2 (Directed to ONE step 1 agent)	Step 3a (Directed to TWO step 1 agents)	Step 3b (Directed to TWO agents from step 1 and/or step 2)	Step 3c (Directed to THREE step 1 agents)
	Step 1a	Step 1b (Directed to ONE TNF inhibitor) NOTE: Please see Step 1a for preferred TNF inhibitors				
Rheumatoid Disorders						
Ankylosing Spondylitis (AS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Enbrel, Hadlima, Humira	Oral: **Rinvoq**, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Simponi, Taltz	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Nonradiographic Axial Spondyloarthritis (nr-axSpA)	SQ: Cimzia, Cosentyx	Oral: **Rinvoq**	N/A	SQ: Taltz	N/A	N/A
Polyarticular Juvenile Idiopathic Arthritis (PJIA)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Enbrel, Hadlima, Humira	Oral: Xeljanz	SQ: Actemra (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	N/A	SQ: Orencia	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**

Psoriatic Arthritis (PsA)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Enbrel, Hadlima, Humira, Skyrizi, Stelara, Tremfya Oral: Otezla	Oral: **Rinvoq**, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Orencia, Simponi, Taltz	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Rheumatoid Arthritis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Enbrel, Hadlima, Humira	Oral: **Rinvoq**, Xeljanz, Xeljanz XR	SQ: Actemra (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	Oral: Olumiant SQ: Cimzia, Kevzara, Kineret, Orencia, Simponi	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Dermatological Disorders						
Hidradenitis Suppurativa (HS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Hadlima, Humira	N/A	N/A	N/A	N/A	N/A
Psoriasis (PS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Enbrel, Hadlima, Humira, Skyrizi, Stelara, Tremfya	N/A	N/A	SQ: Cimzia	N/A	SQ: Abrilada**, Bimzelx, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**,

	Oral: Otezla					Idacio**, Siliq, Taltz, Yuflyma**, Yusimry** Oral: Sotyktu
Inflammatory Bowel Diseases						
Crohn's Disease	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Skyrizi, Stelara	Oral: **Rinvoq**	N/A	SQ: Cimzia (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira are required Step 1 agents)	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Ulcerative Colitis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Stelara	Oral: **Rinvoq**, Xeljanz, Xeljanz XR	SQ: Simponi (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	N/A	Zeposia (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Rinvoq, Stelara, OR Xeljanz/Xeljanz XR are required Step agents)	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Entyvio, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry** Oral: Velsipity
Other						
Uveitis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira	N/A	N/A	N/A	N/A	SQ: Abrilada**, Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**,

						Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Indications Without Prerequisite Biologic Immunomodulators						
Alopecia Areata (AA) Atopic Dermatitis Deficiency of IL-1 Receptor Antagonist (DIRA) Enthesitis Related Arthritis (ERA) Giant Cell Arteritis (GCA) Neonatal-Onset Multisystem Inflammatory Disease (NOMID) Polymyalgia Rheumatica (PMR) Systemic Juvenile Idiopathic Arthritis (SJIA) Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)	N/A	N/A	N/A	N/A	N/A	N/A

*__Note__: A trial of either or both Xeljanz products (Xeljanz and Xeljanz XR) collectively counts as **ONE** product

****Note**: Amjevita (one of: 10 mg/0.2 mL, 20 mg/0.4 mL, 40 mg/0.8 mL), Hadlima, and Humira are required Step 1 agents

Note: Branded generic available for Cyltezo, Hulio, Hyrimoz, and Idacio and are included as a target at same step level in this program

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. Information has been provided that indicates 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 2, 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

2. 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, nr-axSpA, PsA or RA) or the prescriber has consulted with a specialist in the area of the member's diagnosis
3. Member does **NOT** have any FDA labeled contraindications to upadacitinib
4. Member has been tested for latent tuberculosis (TB) **AND**, if positive, the member has begun therapy for latent TB
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), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
6. **ANY** of the following ("a". "b", or "c"):
   a. **EITHER** of the following based on indication:
      i. Atopic dermatitis - the dosage 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 does not exceed 45 mg once daily for 12 weeks
            - QL: 45 mg tablet – 84 tablets/365 days
         b. Maintenance - the dosage does not exceed 30 mg once daily
            - QL: 15 mg tablet - 1 tablet/day
            - QL: 30 mg tablet – 1 tablet/day
      iii. Ulcerative colitis
         a. Induction - the dosage does not exceed 45 mg once daily for 8 weeks
            - QL: 45 mg tablet – 56 tablets/365 days
         b. Maintenance - the dosage does not exceed 30 mg once daily
            - QL: 15 mg tablet - 1 tablet/day
            - QL: 30 mg tablet – 1 tablet/day
      iv. Other indications - the dosage does not exceed 15 mg once daily
         - QL: 15 mg tablet - 1 tablet/day
   b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose **OR** the maximum compendia-supported dose (i.e., DrugDex with 1

or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) 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

c. The requested quantity (dose) exceeds the program quantity limit and exceeds the maximum FDA labeled dose **AND** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the prescriber has provided information in support of therapy with a higher dose for the requested indication (submitted copy required, e.g., clinical trials, phase III studies, guidelines required)

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 2

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) for at least 3 months **OR** b. The member has tried and had an inadequate response to another 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** of the following conventional agents (i.e., maximally tolerated methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** d. The member has an FDA labeled contraindication to **ALL** of the following 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 **ANY** of the following for at least 3 months: • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Enbrel (etanercept) • Hadlima (adalimumab-bwwd) • Humira (adalimumab) **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 a TNF inhibitor for RA **OR** c. The member has an FDA labeled contraindication to **ALL** TNF inhibitors for RA **OR** d. The prescriber has provided information indicating why **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 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 for at least 3 months **OR** b. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of PsA **OR** c. The member has an FDA labeled contraindication to **ALL** of the 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], 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 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 **ANY** of the following for at least 3 months: • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Enbrel (etanercept) • Hadlima (adalimumab-bwwd) • Humira (adalimumab) **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 a TNF inhibitor for PsA **OR** c. The member has an FDA labeled contraindication to **ALL** TNF inhibitors for PsA **OR** d. The prescriber has provided information indicating why **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)	**ALL** of the following: 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. **ONE** of the following: a. The member has tried and had an inadequate response to at least a mid-potency topical steroid used in the treatment of AD for a minimum of 4 weeks **OR** b. The member has an intolerance or hypersensitivity to at least a mid-potency topical steroid used in the treatment of AD **OR** c. The member has an FDA labeled contraindication to **ALL** mid-, high-, and super-potency topical steroids used in the treatment of AD **AND** 3. **ONE** of the following: a. The member has tried and had an inadequate response to a topical calcineurin inhibitor (e.g., Elidel/pimecrolimus, Protopic/tacrolimus) used in the treatment of AD for a minimum of 6 weeks **OR** b. The patient has an intolerance or hypersensitivity to a topical calcineurin inhibitor **OR** c. The patient has an FDA labeled contraindication to ALL topical calcineurin inhibitors **AND** 4. **ONE** of the following: a. The member has tried and had an inadequate response to a systemic immunosuppressant, including a biologic, used in the treatment of AD for a minimum of 3 months **OR**

	b. The member has an intolerance or hypersensitivity to therapy with systemic immunosuppressants, including a biologic, used in the treatment of AD **OR** c. The member has an FDA labeled contraindication to **ALL** systemic immunosuppressants, including biologics, used in the treatment of AD **AND** 5. The prescriber has documented the member's baseline pruritus and other symptom severity (e.g., erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification) **AND** 6. **BOTH** of the following: a. The member is currently treated with topical emollients and practicing good skin care **AND** b. The member will continue the use of topical emollients and good skin care practices in combination with the requested agent
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 for at least 3 months **OR** b. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of UC **OR** c. The member has an FDA labeled contraindication to **ALL** of the 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 Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), **OR** Humira (adalimumab) for at least 3 months **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 Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), OR Humira (adalimumab) **OR** c. The member has an FDA labeled contraindication to Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), **AND** Humira (adalimumab) **OR** d. The prescriber has provided information indicating why Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), AND Humira (adalimumab) 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 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 for at least 3 months **OR** b. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of CD **OR** c. The member has an FDA labeled contraindication to **ALL** of the 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 Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), **OR** Humira (adalimumab) for at least 3 months **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 Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), **OR** Humira (adalimumab) **OR** c. The member has an FDA labeled contraindication to Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), AND Humira (adalimumab) **OR** d. The prescriber has provided information indicating why Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), **AND** Humira (adalimumab) are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication
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 for at least a 4-week total trial **OR** b. The member has an intolerance or hypersensitivity to **TWO** different NSAIDs used in the treatment of AS **OR**

	c. The member has an FDA labeled contraindication to **ALL** NSAIDs used in the treatment of AS **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 AS **AND** 2. **ANY** of the following: a. The member has tried and had an inadequate response to **ANY** of the following for at least 3 months: • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Enbrel (etanercept) • Hadlima (adalimumab-bwwd) • Humira (adalimumab) **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 a TNF inhibitor for AS **OR** c. The member has an FDA labeled contraindication to **ALL** TNF inhibitors for AS **OR** d. The prescriber has provided information indicating why **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 for at least a 4-week total trial **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 Cimzia (certolizumab pegol) for at least 3 months **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 Cimzia (certolizumab pegol) **OR** c. The member has an FDA labeled contraindication to Cimzia (certolizumab pegol) **OR** d. The prescriber has provided information indicating why Cimzia (certolizumab pegol) not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication
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 "6"):

1. An authorization or reauthorization for upadacitinib has been previously approved by Florida Blue
2. **ONE** of the following:
    a. Member had a diagnosis of moderate to severe atopic dermatitis, **AND BOTH** of the following:
        i. The member has had a reduction or stabilization from baseline (prior to therapy with upadacitinib) of **ONE** of the following:
            - Affected body surface area
            - Flares

- Pruritus, erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification
- A decrease in the Eczema Area and Severity Index (EASI) score
- A decrease in the Investigator Global Assessment (IGA) score

AND

ii. The member will continue standard maintenance therapies (e.g., topical emollients, good skin care practices) in combination with upadacitinib

b. All other indications - Member has had clinical benefit with upadacitinib therapy

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 of UC, rheumatologist for AS, nr-axSpA, 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), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
6. **ANY** of the following ("a". "b", or "c"):
   a. **EITHER** of the following based on indication:
      i. Atopic dermatitis, Crohn's disease, and ulcerative colitis - the dosage does not exceed 30 mg once daily
         - QL: 15 mg tablet - 1 tablet/day
         - QL: 30 mg tablet - 1 tablet/day

      ii. Other indications - the dosage does not exceed 15 mg once daily
         - QL: 15 mg tablet - 1 tablet/day

   b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose **OR** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) 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
   c. The requested quantity (dose) exceeds the program quantity limit and exceeds the maximum FDA labeled dose **AND** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the prescriber has provided information in support of therapy with a higher dose for the requested indication (submitted copy required, e.g., clinical trials, phase III studies, guidelines required)

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.
- Treatment of adults 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 dose 15 mg once daily with or without food. May be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs.
- 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.
    - 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.
    - 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 15 mg once daily with or without food.
- 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 15 mg once daily with or without food.

Dose Adjustments

- Renal Impairment - No dose adjustment is required in patients with mild, moderate or severe renal impairment for the treatment of AS, nr-axSpA, RA 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, nr-axSpA, RA, 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). Upadacitinib 15 mg should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors. For patients with atopic dermatitis, coadministration of upadacitinib 30 mg once daily with strong CYP3A4 inhibitors is not recommended. 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

- 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.

PRECAUTIONS:

Boxed Warning

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

- SERIOUS INFECTIONS
  - Patients treated with Rinvoq 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 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 use and during therapy. Treatment for latent infection should be considered prior to Rinvoq 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 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, 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 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 with JAK inhibitors used to treat inflammatory conditions. 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 in patients at risk. Patients with symptoms of thrombosis should discontinue Rinvoq and be promptly evaluated.

Contraindications

- Patients with known hypersensitivity to upadacitinib or any of its excipients

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 – M05.79	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80 – M05.89	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00 – M06.09	Rheumatoid arthritis without rheumatoid factor
M06.20 – M06.29	Rheumatoid bursitis
M06.30 – M06.39	Rheumatoid nodule
M06.80 – M06.89	Other specified rheumatoid arthritis
M06.9	Rheumatoid arthritis, unspecified
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.

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

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 (Humira), 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 [infliximab (Remicade), infliximab-dyyb (Inflectra®), and infliximab-abda (Renflexis)], 09-J0000-39
Ixekizumab (Taltz), 09-J2000-62
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 (Actemra) Injection, 09-J1000-21
Tofacitinib (Xeljanz, Xeljanz XR) Oral Solution, Tablet and Extended-Release Tablet, 09-J1000-86
Ustekinumab (Stelara), 09-J1000-16
Vedolizumab (Entyvio) Injection, 09-J2000-18

OTHER:

Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy

Abrilada (adalimumab-afzb)
Actemra (tocilizumab)
Adalimumab
Adbry (tralokinumab-ldrm)
Amjevita (adalimumab-atto)
Arcalyst (rilonacept)
Avsola (infliximab-axxq)
Benlysta (belimumab)
Bimzelx (bimekizumab-bkzx)
Cimzia (certolizumab)
Cinqair (reslizumab)
Cosentyx (secukinumab)
Cyltezo (adalimumab-adbm)
Dupixent (dupilumab)
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Hadlima (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)

Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Nucala (mepolizumab)
Omvoh (mirikizumab-mrkz)
Orencia (abatacept)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Siliq (brodalumab)
Simponi (golimumab)
Simponi Aria (golimumab)
Skyrizi (risankizumab-rzaa)
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tysabri (natalizumab)
Wezlana (ustekinumab-auub)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zymfentra (infliximab-dyyb)

Table 3: 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 4: 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 11/08/23.

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.