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Subject: Tofacitinib (Xeljanz®, Xeljanz® XR) Oral Solution, Tablet, and Extended-Release Tablet

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DESCRIPTION:

Tofacitinib (Xeljanz) is a novel oral Janus kinase (JAK) inhibitor that was approved by the US Food and Drug Administration (FDA) in November 2012 for the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate. An extended-release formulation of tofacitinib (Xeljanz XR) was approved by the FDA in February 2016 for the same indication. In December 2017 both Xeljanz and Xeljanz XR were FDA-approved for the treatment of adults with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to methotrexate or other DMARDs. The efficacy of tofacitinib as monotherapy in psoriatic arthritis was not studied. In May 2018, Xeljanz (but not Xeljanz XR) was FDA-approved for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). In July 2019, the UC indication was modified to only include patients who have had an inadequate response or who are intolerant to TNF blockers. This change was based on new safety data and boxed warning regarding a higher rate of all-cause mortality and thrombosis observed with the use of 10 mg twice daily in a post-marking study of RA patient with CV risk factors. In December 2019, Xeljanz XR was approved for use in UC (with the same indication as the IR version) and at the same time a new 22 mg dosage strength was introduced for the UC indication. In September 2020, Xeljanz tablets and a new Xeljanz oral solution were approved for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older. The JAK family of kinases plays an important role in cytokine induced signal transduction. Tofacitinib preferentially inhibits JAK1 and JAK3, which ultimately blocks signaling for several cytokines that are integral to lymphocyte activation, proliferation, and function. It is hypothesized that this inhibition results in the modulation of multiple aspects of immune response that play a role in the pathophysiology of RA. 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 all tofacitinib formulations and all indications (RA, PsA, UC, and pcJIA) to require an inadequate response or intolerance to one or more TNF blockers. While some of this safety data was already included, the Boxed Warnings were updated to include additional safety information. Also, in December 2021, the FDA approved, for both Xeljanz tablets and Xeljanz XR tablets, the new indication of treatment of adult patients with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to one or more TNF blockers. In October 2025, the FDA approved an expanded indication for Xeljanz tablets and oral solution to include pediatric patients 2 years of age and older for the treatment of PsA. The National Comprehensive Cancer Network (NCCN) guidelines on the Management of Immune Checkpoint Inhibitor -Related-Toxicities include tofacitinib as a consideration for the management of immunotherapy-related, infliximab- and/or vedolizumab-refractory mild (Grade 1) diarrhea or colitis if persistent or progressive symptoms and positive lactoferrin/calprotectin, and moderate (Grade 2) or severe (Grade 3 to 4) diarrhea or colitis.

RHEUMATOID DISORDERS

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 mainstay of treatment has 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.

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.

INFLAMMATORY BOWEL DISEASE

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:

General treatment information:

- 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

Corticosteroid therapy:

- 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

Disease modifying antirheumatic drug (DMARD) therapy:

- 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:

<u>General treatment information</u>:

- 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

<u>DMARD therapy</u>:

- 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

<u>Advanced therapy</u>:

- 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

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration 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 tofacitinib (Xeljanz) or tofacitinib extended release (Xeljanz XR) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "**5**"):

1. **ONE** of the following ("a", "b", or "c"):
   a. The member has been treated with tofacitinib or tofacitinib ER (starting on samples is not approvable) within the past 90 days

b. The prescriber states the member has been treated with tofacitinib or tofacitinib ER (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. Tofacitinib or tofacitinib ER 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 tofacitinib or tofacitinib ER

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

2. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for AS, JIA, PsA, RA; gastroenterologist for UC) 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 tofacitinib or tofacitinib ER

4. Member will **NOT** be using tofacitinib or tofacitinib ER in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib) and Rinvoq/Rinvoq LQ (upadacitinib)]; Otezla/Otezla XR (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]

5. **ANY** of the following ("a" to "f"):

a. **ANY** of the following depending on the dosage form:

i. Xeljanz tablet - the dosage does not exceed 10 mg twice daily for a maximum of 16 weeks (112 days) [induction therapy for UC], then 5 mg twice daily

- QL: 5 mg tablet - 2 tablets/day
- QL: 10 mg tablet - 240 tablets/365 days

ii. Xeljanz XR tablet - the dosage does not exceed 22 mg once daily for a maximum of 16 weeks (112 days) [induction therapy for UC], then 11 mg once daily

- QL: 11 mg tablet - 1 tablet/day
- QL: 22 mg tablet - 120 tablets/365 days

iii. Xeljanz oral solution – the dosage does not exceed the following based on body weight:

- 10 kg to <20 kg: 3.2 mg (3.2 mL oral solution) twice daily
  - QL: 240 mL/30 days
- 20 kg to <40 kg: 4 mg (4 mL oral solution) twice daily
  - QL: 240 mL/30 days
- 40 kg or more: 5 mg (5 mL oral solution) twice daily
  - QL – 240 mL/30 days, see requirement 6c

b. If the requested agent is Xeljanz/Xeljanz XR for a diagnosis of UC - **BOTH** of the following ('i" and 'ii"):

   i. The prescriber has provided information in support of therapy for the dose exceeding the quantity limit [e.g., patient has lost response to the FDA labeled maintenance dose (i.e., 5 mg twice daily or 11 mg once daily) during maintenance treatment; requires restart of induction therapy] (medical records required)

   ii. 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. If the requested agent is Xeljanz oral solution for a diagnosis of PJIA or PsA - **EITHER** of the following ('i" or 'ii"):

   i. The requested quantity (dose) does not exceed the maximum labeled dose (i.e., 5 mg twice daily), **AND** the prescriber has provided information stating why the member cannot take Xeljanz 5 mg tablets

   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)

d. If the requested agent is **NOT** Xeljanz/Xeljanz XR for a diagnosis of UC, PsA, or PJIA, 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)

e. 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)

f. 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:

- Ulcerative colitis – 16 weeks
- All other indications – 12 months

Table 1

Diagnosis	Criteria
Moderately to severely active rheumatoid arthritis (RA) [Xeljanz and Xeljanz XR tablets only]	**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 after at least a 3-month duration of therapy **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) [Xeljanz and Xeljanz XR tablets only for adults, Xeljanz tablet and Xeljanz oral solution only for pediatric patients]	**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 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 products for the requested indication
Moderately to severely active ulcerative colitis (UC) [Xeljanz and Xeljanz XR tablets only]	**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** TNF inhibitor for UC after at least a 3-month duration of therapy [preferred TNF inhibitors include - Adalimumab-aaty, Adalimumab-adaz, 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 UC **OR** c. The member has an FDA labeled contraindication to to **ALL** TNF inhibitors for UC **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 ankylosing spondylitis (AS) [Xeljanz and Xeljanz XR tablets only]	**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 products for the requested indication
Moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) [Xeljanz tablet and Xeljanz oral solution only]	**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 agent 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 products 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 tofacitinib (Xeljanz) and tofacitinib extended release (Xeljanz XR) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for tofacitinib or tofacitinib ER 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 tofacitinib or tofacitinib ER therapy
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for AS, JIA, PsA, RA; gastroenterologist for UC) 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 tofacitinib or tofacitinib ER
5. Member will **NOT** be using tofacitinib or tofacitinib ER in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib) and Rinvoq/Rinvoq LQ (upadacitinib)]; Otezla/Otezla XR (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
6. **ANY** of the following ("a" to "e"):
    a. **ANY** of the following depending on the dosage form:
        i. Xeljanz tablet - the dosage does not exceed 10 mg twice daily for a maximum of 16 weeks (112 days) [induction therapy for UC], then 5 mg twice daily
            - QL: 5 mg tablet - 2 tablets/day
            - QL: 10 mg tablet - 240 tablets/365 days

ii. Xeljanz XR tablet - the dosage does not exceed 22 mg once daily for a maximum of 16 weeks (112 days) [induction therapy for UC], then 11 mg once daily

- QL: 11 mg tablet - 1 tablet/day
- QL: 22 mg tablet - 120 tablets/365 days

iii. Xeljanz oral solution – the dosage does not exceed the following based on body weight:

- 10 kg to <20 kg: 3.2 mg (3.2 mL oral solution) twice daily
  - QL: 240 mL/30 days
- 20 kg to <40 kg: 4 mg (4 mL oral solution) twice daily
  - QL: 240 mL/30 days
- 40 kg or more: 5 mg (5 mL oral solution) twice daily
  - QL – 240 mL/30 days, see requirement 6c

b. If the requested agent is Xeljanz/Xeljanz XR for a diagnosis of UC - **BOTH** of the following ('i" and 'ii"):

i. The prescriber has provided information in support of therapy for the dose exceeding the quantity limit [e.g., patient has lost response to the FDA labeled maintenance dose (i.e., 5 mg twice daily or 11 mg once daily) during maintenance treatment; requires restart of induction therapy] (medical records required)

ii. 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. If the requested agent is Xeljanz oral solution for a diagnosis of PJIA or PsA - **EITHER** of the following ('i" or 'ii"):

i. The requested quantity (dose) does not exceed the maximum labeled dose (i.e., 5 mg twice daily), **AND** the prescriber has provided information stating why the member cannot take Xeljanz 5 mg tablets

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)

d. If the requested agent is **NOT** Xeljanz/Xeljanz XR for a diagnosis of UC, PsA, or PJIA, 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)
e. 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)
f. 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)

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

FDA-approved:

- Tofacitinib is indicated for: (1) the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers (Xeljanz tablets and Xeljanz XR tablets); (2) the treatment of adult and pediatric patients 2 years of age with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers (Xeljanz oral soluition and tablets and Xeljanz XR tablets; Xeljanz XR is only indicated for adults), and (3) the treatment of adult patients with moderately to severely active ulcerative colitis, who have had an inadequate response or who are intolerant to one or more TNF blockers (Xeljanz tablets and Xeljanz XR tablets), (4) the treatment of pediatric patients 2 years of age and older with active polyarticular course juvenile idiopathic arthritis (pcJIA) who have had an inadequate response or intolerance to one or more TNF blockers (Xeljanz tablets and Xeljanz oral solution), and (5) the treatment of adult patients with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to one or more TNF blockers (Xeljanz tablets and Xeljanz XR tablets).
- For ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis in adults the recommended dose is 5 mg orally twice daily for the immediate-release (IR) tablet (Xeljanz) and 11 mg orally once daily for the extended–release (ER) tablet (Xeljanz XR). For ulcerative colitis in adults the recommended induction dose is 10 mg twice daily of the IR tablet and 22 mg once daily for the ER tablet for at least 8 weeks; evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed, continue 10 mg IR tablet twice daily or 22 mg ER tablet once daily for a maximum of 16 weeks. Discontinue after 16 weeks of treatment, if adequate therapeutic benefit is not achieved. The recommended maintenance dose is 5 mg IR tablet twice daily or 11 mg ER tablet once daily. Use of the 10 mg IR tablet twice daily or 22 mg ER tablet once daily beyond induction should be limited to those with loss of response and used for the shortest duration, with careful consideration of the benefits and risks for the individual patient. Use the lowest effective dose needed to maintain response. For pediatric patients 2 years of age and older with psoriatic arthritis or pcJIA, the recommended dosage is as follows based on body weight - 10 kg to <20 kg: 3.2 mg oral solution twice daily, 20 kg to <40 kg: 4 mg oral solution twice daily, and ≥40 kg: 5 mg (tablet or oral solution) twice daily.
- Tofacitinib should not be used in combination with biologic DMARDs (e.g., tumor necrosis factor alpha inhibitors) or potent immunosuppressants such as azathioprine and cyclosporine. Tofacitinib should not be initiated in members with a lymphocyte count less than 500 cells/mm^3, an absolute neutrophil count less than 1000 cell/mm^3, or a hemoglobin level less than 9 g/dL.

Dose Adjustments

- **Renal Impairment**
  - Mild renal impairment: no dosage adjustment required
  - Moderate to severe renal impairment: If taking 3.2, 4, or 5 mg BID reduce dose to 3.2, 4, or 5 mg once daily, respectively; if taking 10 mg BID reduce to 5 mg BID (IR tablet), if taking 22 mg once daily reduce to 11 mg once daily, if taking 11 mg once daily (XR tablet) switch to 5 mg once daily (IR tablet). For patients undergoing hemodialysis, dose should be administered after the dialysis session on dialysis days.

- **Hepatic Impairment**
  - Mild impairment (Child-Pugh class A, total score of 5 or 6): no dosage adjustment required
  - Moderate impairment (Child-Pugh class B, total score of 7-9): If taking 3.2, 4, or 5 mg BID reduce dose to 3.2, 4, or 5 mg once daily, respectively; if taking 10 mg BID reduce to 5 mg BID (IR tablet), if taking 22 mg once daily reduce to 11 mg once daily, if taking 11 mg once daily (XR tablet) switch to 5 mg once daily (IR tablet)
  - Severe impairment (Child-Pugh class C, total score greater than 10): not recommended
- **Drug Interactions**
  - Strong CYP3A4 inhibitors (e.g., ketoconazole): If taking 3.2, 4, or 5 mg BID reduce dose to 3.2, 4, or 5 mg once daily, respectively; if taking 10 mg BID reduce to 5 mg BID (IR tablet), if taking 22 mg once daily reduce to 11 mg once daily, if taking 11 mg once daily (XR tablet) switch to 5 mg once daily (IR tablet)
  - Concomitant moderate CYP3A4 inhibitor AND strong CYP2C19 (e.g., fluconazole): If taking 3.2, 4, or 5 mg BID reduce dose to 3.2, 4, or 5 mg once daily, respectively; if taking 10 mg BID reduce to 5 mg BID (IR tablet), if taking 22 mg once daily reduce to 11 mg once daily, if taking 11 mg once daily (XR tablet) switch to 5 mg once daily (IR tablet)
- **Therapeutic Drug Monitoring:** recommended dose adjustments for adverse effects are located in Table 2.

Table 2:

Dose adjustments	
Lab Value	**Recommendation**
Lymphopenia	
Lymphocyte count 500 cells/mm^3 or greater	Maintain dose
Lymphocyte count less than 500 cells/mm^3	Discontinue tofacitinib
Neutropenia	
ANC greater than 1000 cells/mm^3	Maintain dose
ANC 500 to 1000 cells/mm^3	• If taking 3.2, 4, or 5 mg BID (IR) or 11 mg once daily (ER): interrupt dosing until ANC is greater than 1000 cells/mm^3 then reinitiate tofacitinib at 3.2, 4, or 5 mg twice daily (IR), respectively; or 11 mg once daily (ER) • If taking 10 mg BID (IR): reduce to 5 mg twice daily. When ANC is greater than 1000, increase to 10 mg twice daily based on clinical response. • If taking 22 mg once daily (ER): reduce to 11 mg once daily. When ANC is greater than 1000, increase to 22 mg once daily based on clinical response.

ANC less than 500 cells/mm^3	Discontinue tofacitinib
Anemia	
Hgb less than or equal to 2 g/dL decrease and greater than or equal to 9 g/dL	Maintain dose
Greater than 2 g/dL decrease or less than 8 g/dL	Interrupt until Hgb values have normalized
ANC, absolute neutrophil count; Hgb, hemoglobin	

Drug Availability:

- Xeljanz - available as white 5-mg and blue 10-mg immediate-release, film-coated tablets
- Xeljanz XR – available as a pink 11-mg and beige 22-mg extended-release tablet
- Xeljanz Oral Solution – available as a 1 mg/mL clear, colorless solution in 240 mL-filled bottles

PRECAUTIONS:

Boxed Warning

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

- SERIOUS INFECTIONS
    - Patients treated with Xeljanz/Xeljanz XR/Xeljanz Oral Solution are at increased risk for developing serious bacterial, fungal, viral, and opportunistic infections, including tuberculosis (TB), that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Reported infections include:
        - Active TB, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Xeljanz/Xeljanz XR /Xeljanz Oral Solution use and during therapy. Treatment for latent infection should be initiated prior to Xeljanz/Xeljanz XR/Xeljanz Oral Solution use.
        - Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
        - Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.

    The risks and benefits of Xeljanz/Xeljanz XR/Xeljanz Oral Solution treatment 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 Xeljanz/Xeljanz XR/Xeljanz Oral Solution, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy. If a serious infection develops, interrupt Xeljanz/Xeljanz XR/Xeljanz Oral Solution until the infection is controlled.

- MORTALITY
    - In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular (CV) risk factor comparing Xeljanz tablets 5 mg or 10 mg twice a day to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden CV death, was observed with Xeljanz tablets 5 or 10 mg twice a day. Xeljanz/Xeljanz Oral Solution 10 mg twice daily and Xeljanz XR 22 mg once daily dosages are not recommended for the treatment of RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS), or polyarticular course juvenile idiopathic arthritis (pcJIA).
- MALIGNANCIES
    - Malignancies, including lymphomas and solid tumors, have occurred in patients treated with Xeljanz and other Janus kinase inhibitors used to treat inflammatory conditions. In RA patients, a higher rate of malignancies [excluding non-melanoma skin cancer (NMSC)] was observed in patients treated with Xeljanz tablet 5 mg or10 mg twice a day compared with TNF blockers.

      Lymphomas and lung cancers were observed at a higher rate in patients treated with Xeljanz tablets 5 mg or 10 mg twice a day in RA patients compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.
- MAJOR ADVERSE CARDIOVASCULAR EVENTS
    - RA patients 50 years of age and older with at least one cardiovascular risk factor, treated with Xeljanz tablets 5 mg or 10 mg twice daily, had a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue Xeljanz/Xeljanz XR/Xeljanz Oral Solution in patients that have experienced a myocardial infarction or stroke.
- THROMBOSIS
    - Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, have occurred in patients treated with Xeljanz and other Janus kinase inhibitors used to treat inflammatory condition. Many of these events were serious and some resulted in death. RA patients 50 years of age and older with at least one cardiovascular risk factor treated with Xeljanz tablets 5 mg or 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid Xeljanz/Xeljanz XR/Xeljanz Oral Solution in patients at risk. Discontinue Xeljanz/Xeljanz XR/Xeljanz Oral Solution and promptly evaluate patients with symptoms of thrombosis.

Contraindications

- None

Precautions/Warnings

- **Serious Infections**: see Boxed Warning
- **Increased Risk of Mortality**: see Boxed Warning
- **Malignancy and Lymphoproliferative Disorders**: see Boxed Warning
- **Major Adverse Cardiovascular Events:** see Boxed Warning
- **Thrombosis**: see Boxed Warning

- **Gastrointestinal perforations:** promptly evaluate patients at increased risk for gastrointestinal perforation who present with new onset abdominal symptoms
- **Hypersensitivity**: reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients receiving treatment. Some events were serious.
- **Laboratory Monitoring:** recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids
- **Immunizations:** Avoid use of live vaccines concurrently with tofacitinib
- **Severe hepatic impairment**: not recommended for use in persons with severe hepatic impairment; refer to dosage and administration section for additional information
- **Risk of Gastrointestinal Obstruction with a Non-Deformable Extended-Release Formulation such as Xeljanz XR**: as with any other non-deformable material, caution should be used when administering Xeljanz XR to patients with pre-existing severe gastrointestinal narrowing

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:

K51.00 – K51.919	Ulcerative colitis
K52.1	Toxic gastroenteritis and colitis [for immunotherapy-related diarrhea or colitis ONLY]
L40.50	Arthropathic psoriasis, unspecified
L40.51	Distal interphalangeal psoriatic arthropathy
L40.52	Psoriatic arthritis mutilans
L40.53	Psoriatic spondylitis
L40.59	Other psoriatic arthropathy
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
M45.0 – M45.9	Ankylosing spondylitis
R19.7	Diarrhea, unspecified [for immunotherapy-related diarrhea or colitis ONLY]

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

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

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.

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:

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

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 strikes 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**.**

Ulcerative colitis: a chronic inflammatory disease of the colon that is of unknown cause and is characterized by diarrhea with discharge of mucus and blood, cramping abdominal pain, and inflammation and edema of the mucous membrane with patches of ulceration.

RELATED GUIDELINES:

Abatacept (Orencia), 09-J0000-67
Adalimumab Products, 09-J0000-46
Anakinra (Kineret), 09-J0000-45
Apremilast (Otezla) Tablet, 09-J2000-19
Baricitinib (Olumiant), 09-J3000-10
Certolizumab Pegol (Cimzia), 09-J0000-77
Etanercept (Enbrel), 09-J0000-38
Etrasimod (Velsipity), 09-J4000-72
Golimumab (Simponi, Simponi Aria), 09-J1000-11
Infliximab Products, 09-J0000-39
Ixekizumab (Taltz), 09-J2000-62
Mirikizumab (Omvoh), 09-J4000-71
Rituximab Products, 09-J0000-59
Sarilumab (Kevzara), 09-J2000-87
Secukinumab (Cosentyx), 09-J2000-30
Tildrakizumab-asmn (Ilumya), 09-J3000-04
Tocilizumab Product (Actemra, Tofidence, Tyenne) Injection, 09-J1000-21
Upadacitinib (Rinvoq), 09-J3000-51
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 3: 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 Coverage Committee on 11/12/25.

GUIDELINE UPDATE INFORMATION:

01/15/13	New Medical Coverage Guideline.
09/15/13	Review and revision to guideline; consisting of revising position statement, updating precautions, related guidelines, program exceptions, and references.
01/01/14	Revision to guideline; consisting of revising position statement
04/15/14	Revision to guideline; consisting of revising position statement.

09/15/14	Review and revision to guideline; consisting of revising the position statement, updating coding and references.
09/15/15	Review and revision to guideline; consisting of updating position statement, warnings/precautions, billing/coding, and references.
11/01/15	Revision: ICD-9 Codes deleted.
04/15/16	Revision to guidelines consisting of updates to the description, position statement, dosage/administration, and references (new extended-release formulation)
09/15/16	Review and revision to guideline consisting of updating description, position statement, billing/coding, and references.
10/15/17	Review and revision to guideline consisting of updating description, position statement, definitions, related guidelines, and references
01/01/18	Revision to guideline consisting of updating the preferred self-administered biologic products according to indication for use.
02/15/18	Revision to guideline consisting of updating the description, position statement, dosage/administration, billing/coding, definitions, related guidelines, and references sections based on the new FDA-approved indication of active psoriatic arthritis.
07/01/18	Revision to guideline consisting of updating the position statement.
07/15/18	Revision to guideline consisting of updating the description section, position statement, dosage/administration, warnings/precautions, billing/coding, related guidelines, definitions, and references based on a new FDA-approved indication of ulcerative colitis.
10/15/18	Review and revision to guideline consisting of updating the position statement, definitions, related guidelines, and references.
10/01/19	Review and revision to guideline consisting of updating the position statement, definitions, related guidelines, and references.
10/15/19	Review and revision to guideline consisting of updating the description, position statement, related guidelines, and references.
01/01/20	Revision to guideline consisting of updating the position statement due to changes in preferred and non-preferred products.
04/01/20	Revision to guideline consisting of updating the description section, position statement, dosage/administration section, precautions section, and references due to the approval of Xeljanz XR for the treatment of UC and release of a new Xeljanz XR 22 mg tablet.
07/01/20	Revision to guideline consisting of updating the description, position statement, and definitions.
01/01/21	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding and references.
03/15/21	Revision to guideline consisting of updating Table 1 in the position statement.
09/15/21	Revision to guideline consisting of updating Table 1 in the position statement and Xeljanz XR quantity limit.
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, related guidelines, other section, and references.

02/15/22	Revision to guideline consisting of updating the description, position statement, dosage/administration, billing/coding, and references.
03/15/22	Revision to guideline consisting of updating the position statement and other sections.
05/15/22	Update to Table 1 in Position Statement.
07/15/22	Update to Table 1 and the UC indication in the Position Statement.
09/15/22	Update to Table 1 in Position Statement.
01/01/23	Review and revision to guideline consisting of updating the position statement, other section, and references. New drugs were added to the list of drugs that are not permitted for use in combination.
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 position statement and other section. 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 section (NCCN info), position statement, other section, billing/coding, and references. 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. Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.
07/01/24	Revision to guideline consisting of updating the position statement, related guidelines, and other section. 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 all indications.
01/01/25	Review and revision to guideline consisting of updating the position statement, other section, and references. Adalimumab-aaty and Adalimumab-adaz added among the preferred adalimumab products. Update to original Table 1 which is now a link out from the Position Statement. Table titles updated. Revised wording regarding maximum dosage exceptions. New drugs were added to the list of drugs that are not permitted for use in combination.
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, precautions, and references. New expanded indication for Xeljanz tablets and oral solution to include pediatric patients 2 years of age and older for the treatment of PsA.