09-J1000-86

Original Effective Date: 01/15/13

Reviewed: 11/09/22

Revised: 01/01/23

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

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

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.

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 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) 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 and 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, leflunomide, pamidronate, thalidomide, apremilast) 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

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.[26-28] 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.[27,28] 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.

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 ACR 2019 guidelines recommend the following treatment approach for PJIA:

- NSAIDs are conditionally recommended as adjunct therapy
- 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-TNF biologic if currently treated with first TNF ± DMARD over switching to another TNF (unless the patient had good initial response to first TNF)
        - TNF, 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, 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

INFLAMMATORY BOWEL DISEASE

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[37]:

<u>Induction of remission</u>:

- 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

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 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: Cosentyx, Enbrel, Humira	Oral: Rinvoq, **Xeljanz, Xeljanz XR**	N/A	SQ: Cimzia, Simponi, Taltz	N/A	N/A
Nonradiographic Axial Spondyloarthritis (nr-axSpA)	SQ: Cimzia, Cosentyx	Oral: Rinvoq	N/A	SQ: Taltz	N/A	N/A
Polyarticular Juvenile Idiopathic Arthritis (PJIA)	SQ: Enbrel, Humira	Oral: **Xeljanz**	SQ: Actemra (Humira is required Step 1 agent)	N/A	SQ: Orencia	N/A
Psoriatic Arthritis (PsA)	SQ: Cosentyx, Enbrel, Humira, Skyrizi, Stelara, Tremfya Oral: Otezla	Oral: Rinvoq, **Xeljanz, Xeljanz XR**	N/A	SQ: Cimzia, Orencia, Simponi, Taltz	N/A	N/A

Rheumatoid Arthritis	SQ: Enbrel, Humira	Oral: Rinvoq, **Xeljanz**, **Xeljanz XR**	SQ: Actemra (Humira is required Step 1 agent)	Oral: Olumiant SQ: Cimzia, Kevzara, Kineret, Orencia, Simponi	N/A	N/A
Dermatological Disorders						
Hidradenitis Suppurativa (HS)	SQ: Humira	N/A	N/A	N/A	N/A	N/A
Psoriasis (PS)	SQ: Cosentyx, Enbrel, Humira, Skyrizi, Stelara, Tremfya Oral: Otezla	N/A	N/A	SQ: Cimzia, Ilumya	N/A	SQ: Siliq, Taltz Oral: Sotyktu
Inflammatory Bowel Disease						
Crohn's Disease	SQ: Humira, Skyrizi, Stelara	N/A	N/A	SQ: Cimzia (Humira is a required Step 1 agent)	N/A	N/A
Ulcerative Colitis	SQ: Humira, Stelara	Oral: Rinvoq, **Xeljanz, Xeljanz XR**	SQ: Simponi (Humira is required Step 1 agent)	N/A	Zeposia (Humira, Rinvoq, Stelara, OR Xeljanz/Xeljanz XR are required Step agents)	N/A
Other						
Uveitis	SQ: Humira	N/A	N/A	N/A	N/A	N/A
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) 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

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 "6"):

1. **ONE** of the following ("a", "b", or "c"):
    a. Information has been provided that indicates 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 2, and **ALL** of the indication-specific criteria are met
        ii. **EITHER** of the following ("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
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 has been tested for latent tuberculosis (TB) **AND**, if positive, the member has begun therapy for latent TB
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), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib) and Rinvoq (upadacitinib)]; Otezla (apremilast); Sotyktu (deucravacitinib); or 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 - **ANY** of the following ('i", "ii", or 'iii"):
   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. The requested quantity (dose) is greater than the maximum FDA labeled dose but does **NOT** exceed the maximum compendia supported dose for the requested indication
   iii. The requested quantity (dose) is greater than 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)

d. If the requested agent is **NOT** Xeljanz/Xeljanz XR for a diagnosis of UC or PJIA, the requested quantity (dose) is greater than program's 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

e. If the requested agent is **NOT** Xeljanz/Xeljanz XR for a diagnosis of UC or PJIA, the requested quantity (dose) is greater that the program's quantity limit and greater than 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:

- Ulcerative colitis – 16 weeks

- All other indications – 12 months

Table 2

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) 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 **EITHER** Humira (adalimumab) **OR** Enbrel (etanercept) 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 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) [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., 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 2. **ANY** of the following:

	a. The member has tried and had an inadequate response to **EITHER** Humira (adalimumab) **OR** Enbrel (etanercept) 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 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
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 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 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 Humira (adalimumab) **OR** c. The member has an FDA labeled contraindication Humira (adalimumab) **OR** d. The prescriber has provided information indicating why Humira (adalimumab) is 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) [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 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 **EITHER** Humira (adalimumab) **OR** Enbrel (etanercept) 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 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
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 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 PJIA **OR** c. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of PJIA **OR** d. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PJIA **AND** 2. **ANY** of the following: a. The member has tried and had an inadequate response to **EITHER** Humira (adalimumab) **OR** Enbrel (etanercept) 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 therapy with a TNF inhibitor for PJIA

	OR c. The member has an FDA labeled contraindication to **ALL** TNF inhibitors for PJIA **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
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
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), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib) and Rinvoq (upadacitinib)]; Otezla (apremilast); Sotyktu (deucravacitinib); or 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 - **ANY** of the following ('i", "ii", or 'iii"):
   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. The requested quantity (dose) is greater than the maximum FDA labeled dose but does **NOT** exceed the maximum compendia supported dose for the requested indication
   iii. The requested quantity (dose) is greater than 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)

d. If the requested agent is **NOT** Xeljanz/Xeljanz XR for a diagnosis of UC or PJIA, the requested quantity (dose) is greater than program's 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

e. If the requested agent is **NOT** Xeljanz/Xeljanz XR for a diagnosis of UC or PJIA, the requested quantity (dose) is greater that the program's quantity limit and greater than 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:

FDA-approved:

- Tofacitinib is indicated for: (1) the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers. It may be used as monotherapy or in combination with methotrexate or other non-biologic DMARDs (Xeljanz tablets and Xeljanz XR tablets); (2) the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers (Xeljanz tablets and Xeljanz XR tablets), 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 active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older 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 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 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 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 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 Xeljanz/Xeljanz XR/Xeljanz Oral Solution 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 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 treatment with Xeljanz/Xeljanz XR/Xeljanz Oral Solution 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 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 Xeljanz 5 mg twice a day or Xeljanz 10 mg twice a day to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with Xeljanz 5 mg twice a day or Xeljanz 10 mg twice a day. A Xeljanz/Xeljanz Oral Solution 10 mg twice daily (or a Xeljanz XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

- 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 NMSC) was observed in patients treated with Xeljanz 5 mg twice a day or Xeljanz 10 mg twice a day compared with TNF blockers. Lymphomas and lung cancers were observed at a higher rate in patients treated with Xeljanz 5 mg twice a day or Xeljanz 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. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with Xeljanz and concomitant immunosuppressive medications.
- MAJOR ADVERSE CARDIOVASCULAR EVENTS
  - RA patients 50 years of age and older with at least one cardiovascular risk factor, treated with Xeljanz 5 mg twice daily or Xeljanz 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 5 mg twice daily or Xeljanz 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
- **Mortality**: see Boxed Warning
- **Malignancy and Lymphoproliferative Disorders**: see Boxed Warning
- **Thrombosis**: see Boxed Warning
- **Gastrointestinal perforations:** use with caution in members that may be at an increased risk

- **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:** live vaccines should not be given 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
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 – M05.79	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
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

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.

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 (Humira), 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
Golimumab (Simponi, Simponi Aria), 09-J1000-11
Infliximab Products [infliximab (Remicade), infliximab-dyyb (Inflectra), and infliximab-abda (Renflexis)], 09-J0000-39
Ixekizumab (Taltz), 09-J2000-62
Rituximab (Rituxan), 09-J0000-59
Sarilumab (Kevzara), 09-J2000-87
Secukinumab (Cosentyx), 09-J2000-30
Tildrakizumab-asmn (Ilumya), 09-J3000-04
Tocilizumab (Actemra) Injection, 09-J1000-21
Upadacitinib (Rinvoq), 09-J3000-51
Ustekinumab (Stelara), 09-J1000-16

OTHER:

Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy
Actemra (tocilizumab)
Adbry (tralokinumab-ldrm)
Arcalyst (rilonacept)
Avsola (infliximab-axxq)
Benlysta (belimumab)
Cimzia (certolizumab)
Cinqair (reslizumab)
Cosentyx (secukinumab)
Dupixent (dupilumab)
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Humira (adalimumab)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab

Kevzara (sarilumab)
Kineret (anakinra)
Nucala (mepolizumab)
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)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tysabri (natalizumab)
Xolair (omalizumab)

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

REFERENCES:

1. Bansback N, Phibbs CS, Sun H, et al; CSP 551 RACAT Investigators. Triple Therapy Versus Biologic Therapy for Active Rheumatoid Arthritis: A Cost-Effectiveness Analysis. Ann Intern Med. 2017 Jul 4;167(1):8-16.
2. Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumor necrosis factor inhibitors: a randomized phase 3 trial. Lancet 2013;381(9865):451-60.
3. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2022. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 10/25/22.
4. Coates LC, Kavanaugh A, Mease PJ et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis: Treatment Recommendations for Psoriatic Arthritis 2015. Arthritis Rheumatol 2016;68:1060–71.
5. Deodhar A, Sliwinska-Stanczyk P, Xu H, et al. Tofacitinib for the treatment of ankylosing spondylitis: a phase III, randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2021 Apr 27;80(8):1004–13. Epub ahead of print.
6. FDA Orphan Drug Designations and Approvals [Internet]. Washington, D.C. [cited 2022 Oct 25]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/.
7. Feuerstein JD, Isaacs KL, Schneider Y, et al.; AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020 Apr;158(5):1450-1461. 2020 Jan 13.
8. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Eng J Med 2012;367(6):495-507.
9. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2021 Jul;73(7):924-939.
10. Graudal N, Hubeck-Graudal T, Tarp S, et al. Effect of combination therapy on joint destruction in rheumatoid arthritis: a network meta-analysis of randomized controlled trials. PLoS One. 2014 Sep 22;9(9):e106408.
11. Hazelwood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology 2014; doi: 10.1053/j.gastro.2014.10.011.
12. Karlsson JA, Neovius M, Nilsson JA, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in early rheumatoid arthritis: 2-year quality-of-life results of the randomised, controlled, SWEFOT trial. Ann Rheum Dis. 2013 Dec;72(12):1927-33.

13. Krause ML, Amin A, and Makol A. Use of DMARDs and biologics during pregnancy and lactation in rheumatoid arthritis: what the rheumatologist needs to know. Ther Adv Musculoskelet Dis. 2014 Oct; 6(5): 169–184.
14. Lee EB, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014; 370: 2377-86.
15. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 10/25/22.
16. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol 2011;65:137-74.
17. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 10/25/22.
18. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Version 1.2022 – February 28, 2022. Management of Immunotherapy-Related Toxicities. Available at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed 11/3/22.
19. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2022 Apr;74(4):521-537. Epub 2022 Mar 1.
20. Peper SM, Lew R, Mikuls T, et al. Rheumatoid Arthritis Treatment After Methotrexate: The Durability of Triple Therapy Versus Etanercept. Arthritis Care Res (Hoboken). 2017 Oct;69(10):1467-1472.
21. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Rheumatol. 2019 Jun;71(6):846-863. Epub 2019 Apr 25.
22. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019 Mar;114(3):384-413.
23. Scott DL, Ibrahim F, Farewell V, et al. Tumour necrosis factor inhibitors versus combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT non-inferiority randomised controlled trial. BMJ. 2015 Mar 13;350:h1046.
24. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Rheumatol. 2019 Jan;71(1):5-32. Epub 2018 Nov 30.
25. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020 Jun;79(6):685-699. Epub 2020 Jan 22.
26. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. Mar 2013; 65 (3): 559-570.
27. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Eng J Med 2012;367(6):508-19.
28. van Vollenhoven RF, Geborek P, Forslind K, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2-year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012 May 5;379(9827):1712-20.

29. Xeljanz/Xeljanz XR/Xeljanz Oral Solution (tofacitinib) [package insert]. Pfizer Inc. New York (NY): January 2022.
30. Yazici Y, Regens AL. Promising new treatments for rheumatoid arthritis: the kinase inhibitors. Bull NYU Hosp Jt Dis 2011;69(3):233-7.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Coverage Committee on 11/09/22.

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.