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Section:	Prescription Drugs	**Effective Date:**	October 1, 2024
Subsection:	Analgesics and Anesthetics	**Original Policy Date:**	January 18, 2013
Subject:	Xeljanz	**Page:**	1 of 12

Last Review Date: September 6, 2024

Xeljanz

Description

Xeljanz (tofacitinib tablets; oral solution)

Xeljanz XR (tofacitinib extended-release tablets)

Background
Xeljanz/Xeljanz XR (tofacitinib) is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Janus kinase inhibitors inhibit one or more Janus family of enzymes (JAK1, JAK2, JAK3, TYK2), interfering with the JAK-STAT signaling pathway. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression (1).

Regulatory Status
FDA-approved indications: Xeljanz/Xeljanz XR is a Janus kinase (JAK) inhibitor indicated for the treatment of: (1)

1. Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers
2. Adult patients with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to one or more TNF blockers
3. Adult patients with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to one or more TNF blockers

4. Adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response or intolerance to one or more TNF blockers
5. Patients 2 years of age and older with active polyarticular course juvenile idiopathic arthritis (pcJIA) who have had an inadequate response to one or more TNF blockers

Limitations of Use:
Xeljanz/Xeljanz XR should not be used in combination with biological DMARDs or potent immunosuppressants such as azathioprine and cyclosporine (1).

Xeljanz/Xeljanz XR carries several boxed warnings: (1)

1. Serious infections
    a. There is an increased risk of serious infections including tuberculosis and bacterial, invasive fungi, viral and other opportunistic infections that may lead to hospitalization or death. If a serious infection develops, interrupt Xeljanz/Xeljanz XR until the infection is controlled. Prior to the initiation of Xeljanz/Xeljanz XR, a test for latent tuberculosis must be conducted. If the test is positive, start treatment for tuberculosis prior to starting Xeljanz/Xeljanz XR. Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative.
2. Mortality
    a. Rheumatoid arthritis patients with at least one cardiovascular (CV) risk factor had a higher rate of all-cause mortality and thrombosis with Xeljanz 10 mg twice daily vs. 5 mg twice daily or TNF blockers.
3. Malignancies
    a. Lymphoma and other malignancies have been observed in patients treated with Xeljanz/Xeljanz XR. Epstein Barr Virus- associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with Xeljanz/Xeljanz XR and concomitant immunosuppressive medications.
4. Major adverse cardiovascular events (MACE)
    a. RA patients 50 years of age and older with at least one CV risk factor, treated with Xeljanz, had a higher rate of MACE (defined as CV 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 use in patients that have experienced a myocardial infarction or stroke.
5. Thrombosis

a. Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with Xeljanz and other JAK inhibitors used to treat inflammatory conditions.

Pfizer shared results from a post-marketing required safety study of Xeljanz. These results showed a higher occurrence of malignancies and major adverse cardiovascular events (MACE) in those subjects with a higher prevalence of known risk factors (e.g., older age, smoking) (2).

The FDA has alerted the public that a safety clinical trial found an increased risk of blood clots in the lungs and death when a 10 mg twice daily dose of tofacitinib was used in patients with rheumatoid arthritis. FDA has not approved this 10 mg twice daily dose for RA; this dose is only approved in the dosing regimen for patients with ulcerative colitis (3).

The safety and effectiveness of Xeljanz XR have not been established in pediatric patients. The safety and effectiveness of Xeljanz/Xeljanz oral solution in pediatric patients for indications other than pcJIA have not been established (1).

Related policies
Olumiant, Rinvoq

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Xeljanz/Xeljanz XR may be considered **medically necessary** if the conditions indicated below are met.

Xeljanz/Xeljanz XR may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Moderately to severely active rheumatoid arthritis (RA)
    a. 18 years of age or older

   b. Inadequate treatment response, intolerance, or contraindication to a 3-month trial of at least **ONE** conventional disease-modifying antirheumatic drug (DMARD) (see Appendix 1)
   c. Inadequate treatment response, intolerance, or contraindication to at least **ONE** TNF blocker (e.g., Cimzia, Enbrel, Humira, Remicade, Simponi/Simponi Aria)
   d. Blue Focus **only:** Patient **MUST** have tried **ONE** of the preferred products (Enbrel or Humira) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

2. Active psoriatic arthritis (PsA)
   a. 18 years of age or older
   b. Used in combination with a nonbiologic disease-modifying antirheumatic drug (DMARD) such as methotrexate, leflunomide, sulfasalazine, etc.
   c. Inadequate treatment response, intolerance, or contraindication to a 3-month trial of at least **ONE** conventional disease-modifying antirheumatic drug (DMARD) (see Appendix 1)
   d. Inadequate treatment response, intolerance, or contraindication to at least **ONE** TNF blocker (e.g., Cimzia, Enbrel, Humira, Remicade, Simponi/Simponi Aria)
   e. Blue Focus **only:** Patient **MUST** have tried **ONE** of the preferred products (Enbrel or Humira) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

3. Active ankylosing spondylitis (AS)
   a. 18 years of age or older
   b. Inadequate treatment response, intolerance, or contraindication to at least **TWO** non-steroidal anti-inflammatory drugs (NSAIDs)
   c. Inadequate treatment response, intolerance, or contraindication to at least **ONE** TNF blocker (e.g., Cimzia, Enbrel, Humira, Remicade, Simponi/Simponi Aria)
   d. Patient **MUST** have tried the preferred product(s) (see Appendix 3) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

4. Moderate to severely active Ulcerative Colitis (UC)
   a. 18 years of age or older

b. Inadequate treatment response, intolerance, or contraindication to at least **ONE** conventional therapy option (see Appendix 2)
c. Inadequate treatment response, intolerance, or contraindication to at least **ONE** TNF blocker (e.g., Humira, Remicade, Simponi)
d. Patient **MUST** have tried Humira unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

5. Active Polyarticular Course Juvenile Idiopathic Arthritis (pcJIA)
   a. 2 years of age or older
   b. Inadequate treatment response, intolerance, or contraindication to a 3-month trial of at least **ONE** conventional disease-modifying antirheumatic drugs (DMARDs) (see Appendix 1)
   c. Inadequate treatment response, intolerance, or contraindication to at least **ONE** TNF blocker (e.g., Enbrel, Humira, Remicade, Simponi Aria)
   d. Blue Focus **only:** Patient **MUST** have tried **ONE** of the preferred products (Enbrel or Humira) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

AND ALL of the following for **ALL** indications:
a. Prescriber has considered the risks for malignancy and major adverse cardiovascular events (MACE) (e.g., advanced age, smoking history, cardiovascular risk factors etc.) and determined that Xeljanz therapy is appropriate
b. Result for latent TB infection is negative **OR** result was positive for latent TB and patient completed treatment (or is receiving treatment) for latent TB
c. **NO** active bacterial, invasive fungal, viral, and other opportunistic infections
d. **NOT** to be used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)
e. **NOT** used in combination with potent immunosuppressants azathioprine or cyclosporine
f. **NOT** given concurrently with live vaccines

AND NONE of the following for **ALL** indications:
a. Severe hepatic impairment
b. A lymphocyte count less than 500 cells/mm3
c. An absolute neutrophil count less than 1000 cells/mm3
d. A hemoglobin less than 9 g/dL

Prior – Approval *Renewal* Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Rheumatoid arthritis (RA)
    a. 18 years of age or older
    b. Blue Focus **only:** Patient **MUST** have tried **ONE** of the preferred products (Enbrel or Humira) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

2. Psoriatic arthritis (PsA)
    a. 18 years of age or older
    b. Used in combination with a nonbiologic disease-modifying antirheumatic drug (DMARD) such as methotrexate, leflunomide, sulfasalazine, etc.
    c. Blue Focus **only:** Patient **MUST** have tried **ONE** of the preferred products (Enbrel or Humira) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

3. Ankylosing spondylitis (AS)
    a. 18 years of age or older
    b. Patient **MUST** have tried the preferred product(s) (see Appendix 3) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

4. Ulcerative Colitis (UC)
    a. 18 years of age or older
    b. Patient **MUST** have tried Humira unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

5. Polyarticular Course Juvenile Idiopathic Arthritis (pcJIA)
    a. 2 years of age or older
    b. Blue Focus **only:** Patient **MUST** have tried **ONE** of the preferred products (Enbrel or Humira) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

AND ALL of the following for **ALL** indications:

a. Condition has improved or stabilized
b. Prescriber has considered the risks for malignancy and major adverse cardiovascular events (MACE) (e.g., advanced age, smoking history, cardiovascular risk factors etc.) and determined that continuation of Xeljanz therapy is appropriate
c. Absence of active bacterial, invasive fungal, viral, and other opportunistic infections
d. **NOT** to be used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)
e. **NOT** used in combination with potent immunosuppressants azathioprine or cyclosporine
f. **NOT** given concurrently with live vaccines

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity

Drug	Diagnosis	Quantity
Xeljanz Oral Solution 1mg/mL	pcJIA	960 mL per 90 days **OR**
Xeljanz 5mg	AS pcJIA PsA RA UC	180 tablets per 90 days **OR**
Xeljanz 10mg	UC	180 tablets per 90 days **OR**
Xeljanz XR 11mg	AS PsA RA UC	90 tablets per 90 days **OR**
Xeljanz XR 22mg	UC	90 tablets per 90 days

Duration 12 months

Prior – Approval *Renewal* Limits

Quantity

Drug	Diagnosis	Quantity
Xeljanz Oral Solution 1mg/mL	pcJIA	960 mL per 90 days **OR**
Xeljanz 5mg	AS pcJIA PsA RA UC	180 tablets per 90 days **OR**
Xeljanz 10mg	UC	180 tablets per 90 days **OR**
Xeljanz XR 11mg	AS PsA RA UC	90 tablets per 90 days **OR**
Xeljanz XR 22mg	UC	90 tablets per 90 days

Duration 18 months

Rationale

Summary

Xeljanz/Xeljanz XR (tofacitinib) is indicated for the treatment of adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), ulcerative colitis (UC), and patients 2 years of age and older with polyarticular course juvenile idiopathic arthritis (pcJIA). Xeljanz/Xeljanz XR has several boxed warnings including increased risk of serious infections, mortality, malignancies, MACE, and thrombosis. The safety and effectiveness of Xeljanz XR have not been established in pediatric patients. The safety and effectiveness of Xeljanz/Xeljanz oral solution in pediatric patients for indications other than pcJIA have not been established (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Xeljanz/Xeljanz XR while maintaining optimal therapeutic outcomes.

References

1. Xeljanz/Xeljanz XR [package insert]. New York, NY: Pfizer Labs; May 2024.
2. Pfizer shares co-primary endpoint results from post-marketing required safety study of Xeljanz (tofacitinib) in subjects with rheumatoid arthritis. January 27, 2021. Accessed at https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing
3. FDA Safety Announcement. Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients. February 25, 2019. Accessed at https://www.fda.gov/Drugs/DrugSafety/ucm631871.htm

Policy History

Date	Action
December 2012	New addition to PA
March 2013	Annual editorial review
September 2013	Annual editorial review and reference update Addition to criteria that the patient must not have any of the following: Severe hepatic impairment, lymphocyte count less than 500 cells/mm3, absolute neutrophil count less than 1000 cells/mm3 and hemoglobin less than 9 grams/dL
September 2014	Annual editorial review and reference update and renewal limit to 18 months
March 2016	Annual editorial review Addition of Xeljanz XR Policy number changed from 5.02.24 to 5.70.24
September 2016	Annual editorial review and reference update Addition of not given concurrently with live vaccines per SME
December 2016	Annual editorial review and reference update
March 2017	Annual review
December 2017	Annual review
January 2018	Addition of new indication of active psoriatic arthritis Addition of Appendix 1- List of DMARDs
March 2018	Annual review
June 2018	Addition of the diagnosis of Ulcerative Colitis (UC) and drug strength 10mg Addition of additional requirements to initiation criteria - For diagnoses of RA: Inadequate response, intolerance, or contraindication to a 3-month trial of at least ONE conventional DMARD - For diagnosis of PsA: inadequate response, intolerance or contraindication to a 3-month trial of at least ONE conventional DMARD Addition of Appendix 2 - List of Conventional Therapies
September 2018	Annual editorial review
March 2019	Annual review and reference update. Addition of the FDA blood clot warning with the 10 mg twice daily dose in RA patients
December 2019	Annual review and reference update. Addition of requirement to trial preferred product
January 2020	Revised dosing for Xeljanz XR for UC and added Xeljanz XR 22mg dosing
March 2020	Annual editorial review. Removed requirement for initiation for UC that if the patient is intolerant or contraindicated to Humira then another TNF blocker needs to be tried. Added requirement for psoriatic arthritis to be used in combination with a nonbiologic DMARD
October 2020	Addition of indication: polyarticular course juvenile idiopathic arthritis (pcJIA). Addition of Xeljanz 1mg/mL oral solution to quantity limit chart

December 2020	Annual review and reference update. Added requirement to t/f preferred products for Blue Focus patients. Added Appendix 3 with a list of preferred medications based on diagnosis and plan
January 2021	Updated t/f options for UC to require trial of Humira first per FEP
March 2021	Annual review
June 2021	Annual review
January 2022	Added t/f requirements for all indications to t/f at least one TNF blocker per package insert update. Added indication: ankylosing spondylitis (AS). Added Xeljanz AS to Medex chart as non-preferred. Added requirement for prescriber to assess risks with malignancy and MACE, per latest PI update. Hemoglobin units updated to g/dL.
March 2022	Annual review and reference update
April 2022	Added Rinvoq as a preferred UC product to chart (Appendix 3)
May 2022	Added Rinvoq as a preferred AS product to chart (Appendix 3)
June 2022	Annual review
September 2022	Annual review
December 2022	Annual review
December 2023	Annual review
March 2024	Annual review
September 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 6, 2024 and is effective on October 1, 2024.

Appendix 1 - List of DMARDs

Conventional disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
azathioprine	Azasan, Imuran
cyclophosphamide	Cytoxan
cyclosporine	Neoral, Gengraf, Sandimmune
hydroxychloroquine	Plaquenil
leflunomide	Arava
methotrexate	Rheumatrex, Trexall
mycophenolate	Cellcept
sulfasalazine	Azulfidine, Sulfazine

Biological disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
abatacept	Orencia
adalimumab	Humira
anakinra	Kineret
brodalumab	Siliq
certolizumab	Cimzia
etanercept	Enbrel
golimumab	Simponi/Simponi Aria
guselkumab	Tremfya
infliximab	Remicade/Renflexis/Inflectra
ixekizumab	Taltz
risankizumab-rzaa	Skyrizi
rituximab	Rituxan
sarilumab	Kevzara
secukinumab	Cosentyx
spesolimab-sbzo	Spevigo
tildrakizumab-asmn	Ilumya
tocilizumab	Actemra
ustekinumab	Stelara
vedolizumab	Entyvio

Targeted synthetic disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
apremilast	Otezla
baricitinib	Olumiant
deucravacitinib	Sotyktu

tofacitinib	Xeljanz
upadactinib	Rinvoq

Appendix 2 - List of Conventional Therapies

Conventional Therapy Options for UC
1. Mild to moderate disease – induction of remission: a. Oral mesalamine (e.g., Asacol, Lialda, Pentasa), balsalazide, olsalazine b. Rectal mesalamine (e.g., Canasa, Rowasa) c. Rectal hydrocortisone (e.g., Colocort, Cortifoam) d. Alternatives: prednisone, azathioprine, mercaptopurine, sulfasalazine
2. Mild to moderate disease – maintenance of remission: a. Oral mesalamine, balsalazide, olsalazine, rectal mesalamine b. Alternatives: azathioprine, mercaptopurine, sulfasalazine
3. Severe disease – induction of remission: a. Prednisone, hydrocortisone IV, methylprednisolone IV b. Alternatives: cyclosporine IV, tacrolimus, sulfasalazine
4. Severe disease – maintenance of remission: a. Azathioprine, mercaptopurine b. Alternative: sulfasalazine
5. Pouchitis: a. Metronidazole, ciprofloxacin b. Alternative: rectal mesalamine

Appendix 3 - List of Preferred Products

Diagnosis	Standard Option/Basic Option Preferred Products	Blue Focus Preferred Products
Ankylosing spondylitis (AS)	*must try **TWO** preferred products: Enbrel Humira** Rinvoq Taltz	*must try **ONE** preferred product: Enbrel Humira**
Ulcerative colitis (UC)	*must try **Humira** first: Humira** Rinvoq Stelara (SC)	Humira**

**Including all preferred biosimilars (see reference product chart)