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Section:	Prescription Drugs	**Effective Date:**	April 1, 2021
Subsection:	Analgesics and Anesthetics	**Original Policy Date:**	January 18, 2013
Subject:	Xeljanz	**Page:**	1 of 10

Last Review Date: March 12, 2021

Xeljanz

Description

Xeljanz, Xeljanz XR (tofacitinib)

Background
Xeljanz and Xeljanz XR (tofacitinib) are inhibitors of Janus kinases (JAKs). 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 indication: Xeljanz and Xeljanz XR are inhibitors of Janus kinases (JAKs) indicated for the treatment of: (1)

1. Adult patients with moderately or severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. Xeljanz and Xeljanz XR may be used as monotherapy or in combination with methotrexate or other **non-biologic** disease-modifying antirheumatic drugs (DMARDs)
2. Adult patients with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs)
3. Adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response or who are intolerant to TNF blockers
4. Patients 2 years of age and older with active polyarticular course juvenile idiopathic arthritis (pcJIA)

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

Xeljanz and Xeljanz XR carries a boxed warning in the label for an increased risk for: 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 until the infection is controlled. Prior to the initiation of Xeljanz or Xeljanz XR, a test for latent tuberculosis must be conducted. If the test is positive, start treatment for tuberculosis prior to starting Xeljanz and Xeljanz XR. Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative (1).

Xeljanz and Xeljanz XR also have boxed warnings regarding 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 (1).

The last boxed warnings are regarding malignancies and thrombosis. Lymphoma and other malignancies have been observed in patients treated with Xeljanz and 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. 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 (1).

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. 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 and Xeljanz XR may be considered **medically necessary** in patients with rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, or polyarticular course juvenile idiopathic arthritis; and if the conditions indicated below are met.

Xeljanz and 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 response, intolerance, or contraindication to a 3-month trial of at least **ONE** conventional disease-modifying antirheumatic drugs (DMARDs) (see Appendix 1)
    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)

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 response, intolerance or contraindication to a 3-month trial of at least **ONE** conventional DMARD (see Appendix 1)
    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)

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

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

4. Active Polyarticular Course Juvenile Idiopathic Arthritis (pcJIA)
   a. 2 years of age or older
   b. Inadequate response, intolerance, or contraindication to a 3-month trial of at least **ONE** conventional disease-modifying antirheumatic drugs (DMARDs) (see Appendix 1)
   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)

AND ALL of the following for **ALL** indications:
   a. 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
   b. **NO** active bacterial, invasive fungal, viral, and other opportunistic infections
   c. **NOT** to be used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)
   d. **NOT** used in combination with potent immunosuppressants azathioprine or cyclosporine
   e. **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 grams

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. 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)
4. 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. Absence of active bacterial, invasive fungal, viral, and other opportunistic infections
c. **NOT** to be used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)
d. **NOT** used in combination with potent immunosuppressants azathioprine or cyclosporine
e. **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	pcJIA PsA RA UC	180 tablets per 90 days **OR**
Xeljanz 10mg	UC	180 tablets per 90 days **OR**
Xeljanz XR 11mg	PsA RA UC	90 tablets per 90 days **OR**
Xeljanz XR 22mg	UC	90 tablets per 90 days

***This strength is included in this policy but is not available in the market as of yet

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	pcJIA PsA RA UC	180 tablets per 90 days **OR**
Xeljanz 10mg	UC	180 tablets per 90 days **OR**
Xeljanz XR 11mg	PsA RA UC	90 tablets per 90 days **OR**
Xeljanz XR 22mg	UC	90 tablets per 90 days

*This strength is included in this policy but is not available in the market as of yet

Duration 18 months

Rationale

Summary

Xeljanz and Xeljanz XR are FDA-approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis (PsA), moderately to severely active ulcerative colitis (UC), or active polyarticular course juvenile idiopathic arthritis (pcJIA). Xeljanz and Xeljanz XR carry a boxed warning due to increased risk of serious infections, mortality, malignancy, and thrombosis (1).

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

References

1. Xeljanz/Xeljanz XR [package insert]. New York, NY: Pfizer Labs; October 2020.
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
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

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.

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
tildrakizumab-asmn	Ilumya
tocilizumab	Actemra
ustekinumab	Stelara
vedolizumab	Entyvio

Targeted synthetic disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
apremilast	Otezla
baricitinib	Olumiant

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
Ulcerative colitis (UC)	*must try **Humira** first: Humira Stelara (SC)	Humira