EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Xeljanz®/Xeljanz XR (tofacitinib tablets/tofacitinib extended-release tablets – Pfizer)

TAC APPROVAL DATE: 06/18/2019; selected revision 07/31/2019

OVERVIEW

Xeljanz/Xeljanz XR is an inhibitor of the Janus kinases (JAK) pathways. Xeljanz and Xeljanz XR are approved for the following indications:

1. Rheumatoid arthritis (RA), for treatment of adults with moderately to severely active disease who have had an inadequate response or intolerance to methotrexate (MTX), either as monotherapy or in combination with MTX or other nonbiologic disease-modifying antirheumatic drugs (DMARDs); AND
2. Psoriatic arthritis (PsA), for treatment of patients who have had an inadequate response or intolerance to MTX or other DMARDs.

Xeljanz is also approved for the following indication:

1. Ulcerative colitis, for treatment of adults with moderately to severely active disease who have had an inadequate response or who are intolerant to tumor necrosis factor inhibitors (TNFis).

For all indications, Xeljanz/XR is not recommended for use in combination with biologics or potent immunosuppressants such as azathioprine or cyclosporine.

The efficacy of Xeljanz over placebo was established in seven pivotal studies that included a variety of clinical scenarios, including Xeljanz as monotherapy or in combination with MTX or other DMARDs and in patients who had failed a TNFi.[1-6] Efficacy studies were not required for approval of Xeljanz XR because it was determined that Xeljanz XR (11 mg once daily) is pharmacokinetically equivalent to Xeljanz 5 mg administered twice daily.[1] In RA and PsA, the recommended dose of Xeljanz is 5 mg twice daily (BID) and the dose of Xeljanz XR is 11 mg once daily. In UC, the dose of Xeljanz is 10 mg BID for at least 8 weeks, then 5 mg or 10 mg BID. In UC, Xeljanz should be discontinued if adequate benefit has not been achieved after 16 weeks of therapy.

Disease Overview

Inflammatory conditions are chronic, systemic, autoimmune, inflammatory disorders of unknown origin characterized by inflammation.[12] RA causes joint swelling, stiffness, and tenderness which may lead to cartilage damage, bone erosions, and joint destruction, and is often associated with significant activity limitations and disability. Compared with patients who do not have RA, mortality is increased in patients with established RA with approximately 40% of deaths in the RA population attributed to cardiovascular causes such as ischemic heart disease or stroke.[13] RA is associated with a decreased quality of life and can contribute to reduced employment rates and increased costs of care.[12] In RA, Xeljanz/Xeljanz XR inhibits JAK, an intracellular enzyme that transmits signals on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function.[1] JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STAT) which then modulate intracellular activity such as gene expression. Inhibition of JAK1 and JAK3 block multiple cytokines resulting in modulation of the immune response involved in RA. Similar to RA, inhibition

of JAKs with Xeljanz/XR modulates psoriatic inflammation in articular and extra-articular locations in patients with PsA.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- Psoriatic Arthritis: Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[4]
- Rheumatoid Arthritis: Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors and non-TNF biologics, administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[5]
- Ulcerative Colitis: Updated ACG guidelines for UC (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris tablets; Oral or intravenous systemic corticosteroids Entyvio, Xeljanz, or TNFis (adalimumab, Simponi SC, infliximab).[6]

Safety

Xeljanz/Xeljanz XR has Boxed Warnings regarding increased risk of developing serious infections which may lead to hospitalization or death.[1] Patients who develop a serious infection should interrupt treatment with Xeljanz/XR until infection is controlled. Patients should be tested for tuberculosis (TB) prior to starting therapy and monitored during treatment with Xeljanz/XR. Lymphoma and other malignancies have been observed in patients taking Xeljanz/XR. Epstein Barr virus-associated post-transplant lymphoproliferative disorder has been observed at a higher rate in patients with a renal transplant who were treated with Xeljanz and concomitant immunosuppressant medications. There is also a Boxed Warning regarding a higher rate of all-cause mortality and thrombosis in patients with RA and at least one cardiovascular risk factor who were taking Xeljanz 10 mg twice daily vs. those taking Xeljanz 5 mg twice daily or TNFis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xeljanz/Xeljanz XR. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xeljanz as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Xeljanz/Xeljanz XR to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xeljanz/Xeljanz XR is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Psoriatic Arthritis (PsA).** Approve Xeljanz or Xeljanz XR for the duration noted if the patient meets ONE of the following criteria (A or B):
   A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, iii, and iv):

i. The patient is an adult greater than or equal to 18 years of age; AND

ii. The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months.
Note: Examples include methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic (e.g., Cimzia [certolizumab pegol SC injection], an etanercept product [e.g., Enbrel], an adalimumab product [e.g., Humira], an infliximab product [e.g., Remicade, Inflectra, Renflexis], Simponi [golimumab SC injection], Simponi Aria [golimumab IV infusion], Orencia [abatacept IV infusion, abatacept SC injection], Cosentyx [secukinumab SC injection], Stelara SC [ustekinumab SC injection], or Taltz [ixekizumab SC injection]). These patients who have already tried a biologic for PsA are not required to "step back" and try a conventional synthetic DMARD); AND

iii. The medication will be used concomitantly with methotrexate or another conventional synthetic DMARD, unless contraindicated.
Note: Examples of other conventional synthetic DMARDs include leflunomide and sulfasalazine; AND

iv. The medication is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Xeljanz/XR. Approve for 3 years if the patient meets BOTH of the following (i and ii):

i. The medication will be used concomitantly with methotrexate or another conventional synthetic DMARD, unless contraindicated;
Note: Examples of other conventional synthetic DMARDs include leflunomide and sulfasalazine AND

ii. The patient has responded as determined by the prescriber.
Note: Examples of a response to therapy include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants (for example, C-reactive protein). The patient may not have a full response, but there should have been a recent or past response to Xeljanz/XR.

2. Rheumatoid Arthritis (RA). Approve Xeljanz or Xeljanz XR for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. The patient is an adult greater than or equal to 18 years of age; AND

ii. The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months.
Note: Examples include methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic (e.g., Cimzia [certolizumab pegol SC injection], an etanercept product [e.g., Enbrel], an adalimumab product [e.g., Humira], an infliximab product [e.g., Remicade, Inflectra, Renflexis], Simponi [golimumab SC injection], Simponi Aria [golimumab IV infusion], Actemra [tocilizumab IV infusion, tocilizumab SC injection], Kevzara [sarilumab SC injection], Kineret [anakinra SC injection], Orencia [abatacept IV infusion, abatacept SC injection], or a rituximab product [e.g., Rituxan, Truxima]). These patients who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD); AND

ii. Xeljanz is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Xeljanz/Xeljanz XR. Approve for 3 years if the patient has had a response, as determined by the prescriber.
Note: Examples of a response to therapy include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Xeljanz/Xeljanz XR.

3. Ulcerative Colitis. Approve Xeljanz (not Xeljanz XR) for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, and iii):
i. The patient is an adult greater than or equal to 18 years of age; AND
ii. The patient has had a trial of at least ONE tumor necrosis factor inhibitor for ulcerative colitis.
Note: Examples of a tumor necrosis factor inhibitor include an adalimumab product (e.g., Humira), an infliximab product (e.g., Remicade, Renflexis, Inflectra), Simponi SC (golimumab SC injection); AND
iii. Xeljanz is prescribed by or in consultation with a gastroenterologist.

B) Patients Currently Receiving Xeljanz. Approve for 3 years if the patient has had a response, as determined by the prescriber.
Note: Examples of a response include decreased stool frequency or rectal bleeding. The patient may not have a full response, but there should have been a recent or past response to Xeljanz.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xeljanz/Xeljanz XR has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Ceularonditions Not Recommended for Approval.)

1. Concurrent Use with a Biologic or with a Targeted Synthetic DMARD. Xeljanz/XR should not be administered in combination with a biologic used for an inflammatory condition (see APPENDIX for examples).[1] Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of evidence supporting additive efficacy.[7-8] There are no data evaluating combination of Xeljanz/XR with a targeted synthetic DMARD (e.g., Otezla); therefore, safety and efficacy of this combination is unknown.

2. Concurrent use with Other Potent Immunosuppressants (e.g., azathioprine, tacrolimus, cyclosporine, mycophenolate mofetil).[1] Coadministration with other potent immunosuppressive drugs has the risk of added immunosuppression and has not been evaluated in RA. In UC, Xeljanz is not recommended for use in combination with potent immunosuppressants such as azathioprine and cyclosporine. Note: This does NOT exclude use of Xeljanz/Xeljanz XR with MTX for RA; Xeljanz/Xeljanz XR has been evaluated in patients with RA taking background MTX, leflunomide, or combinations of DMARDs containing MTX and/or leflunomide.

3. Renal Transplantation. More data are needed. A Phase IIb study in kidney transplant patients (n = 331) found Xeljanz was equivalent to cyclosporine in preventing acute rejection.[9] However,

based on Phase IIb studies, there are concerns of Epstein Barr Virus-associated post-transplant lymphoproliferative disorder (PTLD) in certain transplant patients receiving Xeljanz.[1,9]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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3. Singh JA, Cameron DR. Summary of AHRQ's comparative effectiveness review of drug therapy for rheumatoid arthritis (RA) in adults--an update. *J Manag Care Pharm*. 2012;18(4 Supp C):S1-18.
4. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis. *Arthritis Care Res (Hoboken).* 2019;71(1):2-29.
5. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26.
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7. Furst DE, Keystone EC, So AK, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis*. 2013;72 Suppl 2:ii2-34.
8. Xeljanz® tablets [prescribing information]. New York, NY: Pfizer Inc; February 2016.
9. Vincenti F, Tedesco Silva H, Busque S, et al. Randomized phase 2b trial of tofacitinib (CP-690,550) in de novo kidney transplant patients: efficacy, renal function and safety at 1 year. *Am J Transplant*. 2012;12(9):2446-2456.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	For RA, Kevzara was added as an example of an agent that may have been tried prior to Xeljanz/XR. In addition, Humira, Enbrel, Remicade, and Rituxan were reworded as adalimumab, etanercept, infliximab, and rituximab products, respectively, with the innovator names listed as examples of these products. Renflexis was also added as an example of an infliximab product.	10/11/2017
Selected revision	Add PsA as a new indication. Approve initial therapy for 3 months if the patient has tried a csDMARD for at least 3 months, is concurrently taking a csDMARD (unless intolerant), and if prescribed by or in consultation with a rheumatologist or dermatologist. For patients currently taking, approval is for 3 years if the patient has responded to previous therapy and taking concurrently with a csDMARD (unless intolerant).	01/03/2018
Selected revision	Add targeted synthetic DMARDs as agents that should not be taken concurrently with Xeljanz/XR.	05/09/2018
Early annual revision	For Xeljanz immediate-release, add approval criteria for adults with UC, if a systemic agent has been previously tried and Xeljanz is prescribed by or in consultation with a gastroenterologist. Initial approval is for 4 months; if the patient is currently taking Xeljanz for UC, approval is for 3 years if the patient has responded to therapy. Clarify that other approval conditions apply to both Xeljanz and Xeljanz XR.	06/13/2018
Selected revision	**Ulcerative colitis:** For the requirement that another agent be tried prior to Xeljanx, remove the requirement that the trial is a duration of at least 2 months (not supported in updated guidelines).	03/27/2019
Annual revision	**Rheumatoid arthritis:** Truxima was added as a rituximab product which may have been tried prior to Xeljanz/XR.	06/18/2019
Selected revision	**Ulcerative Colitis:** To align with the updated labeling, revise criteria for UC to approve if the patient has previously tried at least one tumor necrosis factor inhibitor for UC (previously, criteria required a trial of one systemic therapy, unless intolerant). Move the requirement that the patient is an adult into the criteria section for initial therapy. Clarify criteria to require the patient be an adult ≥ 18 years of age. Previously, the requirement that the patient was an adult was listed as part of the diagnosis (i.e., previously listed as ulcerative colitis in an adult) and	07/31/2019

	applied to initial and continuation of therapy. **Rheumatoid Arthritis:** To align with the labeling, limit initial approval to adults ≥ 18 years of age with rheumatoid arthritis. **Psoriatic Arthritis:** To align with the labeling, limit initial approval to adults ≥ 18 years of age with psoriatic arthritis.	

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; TAC – Therapeutic Assessment Committee; RA – Rheumatoid arthritis.

APPENDIX

Brand (generic name)	Mechanism of Action
Cimzia® (certolizumab pegol for SC injection)	Inhibition of TNF
Enbrel® (etanercept for SC injection)	Inhibition of TNF
Erelzi™ (etanercept-szzs for SC injection)	Inhibition of TNF
Humira® (adalimumab for SC injection)	Inhibition of TNF
Amjevita® (adalimumab-atto for SC injection)	Inhibition of TNF
Cyltezo® (adalimumab-adbm for SC injection)	Inhibition of TNF
Simponi® (golimumab for SC injection)	Inhibition of TNF
Simponi® Aria™ (golimumab for IV infusion)	Inhibition of TNF
Remicade® (infliximab for IV infusion)	Inhibition of TNF
Inflectra™ (infliximab-dyyb for IV infusion)	Inhibition of TNF
Renflexis® (infliximab-abda for IV infusion)	Inhibition of TNF
Actemra® (tocilizumab for IV infusion)	Inhibition of IL-6
Actemra® (tocilizumab for SC injection)	Inhibition of IL-6
Kevzara® (sarilumab for SC injection)	Inhibition of IL-6
Orencia® (abatacept for IV infusion)	T-cell costimulation modulator
Orencia® (abatacept for SC injection)	T-cell costimulation modulator
Rituxan® (rituximab for IV infusion)	CD20-directed cytolytic antibody
Truxima® (rituximab-abbs IV injection)	CD20-directed cytolytic antibody
Kineret® (anakinra for subcutaneous SC injection)	Inhibition of IL-1
Stelara® (ustekinumab for SC injection)	Inhibition of IL-12/23
Stelara® (ustekinumab for IV infusion)	Inhibition of IL-12/23
Siliq™ (brodalumab SC injection)	Inhibition of IL-17
Cosentyx™ (secukinumab for SC injection)	Inhibition of IL-17A
Taltz® (ixekizumab for SC injection)	Inhibition of IL-17A
Skyrizi™ (risankizumab SC injection)	Inhibition of IL-23
Tremfya™ (guselkumab for SC injection)	Inhibition of IL-23
Ilumya™ (tildrakizumab-asmn for SC injection)	Inhibition of IL-23
Otezla® (apremilast tablets)	Inhibition of PDE4
Olumiant® (baricitib tablets)	Inhibition of the JAK pathways
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways

SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin;PDE4 – Phosphodiesterase 4; JAK – Janus kinase.