BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Tofacitinib (Xeljanz®)

Policy # 00352
Original Effective Date: 05/22/2013
Current Effective Date: 01/01/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of tofacitinib (Xeljanz®)‡ for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility for tofacitinib (Xeljanz) will be considered when all of the following criteria are met:

- Patient is 18 years of age or older; and
- Patient has a diagnosis of moderately to severely active rheumatoid arthritis (RA); and
- Patient had an inadequate response or intolerance to methotrexate; and
- Tofacitinib (Xeljanz) is NOT being used in combination with biologic disease modifying anti-rheumatic drugs (DMARDs) OR potent immunosuppressants such as azathioprine and cyclosporine; and
- Tofacitinib (Xeljanz) may be used alone or in combination with methotrexate or other NON-biologic DMARDs; and
- Patient has a negative purified protein derivative (PPD) test prior to treatment; and
- Patient has failed treatment with adalimumab (Humira®)‡ AND etanercept (Enbrel®)‡) after at least two months of therapy with each product (unless there is clinical evidence or patient history that suggests that the these products will be ineffective or cause an adverse reaction to the patient)
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of tofacitinib (Xeljanz) when patient selection criteria are not met to be **investigational*** (with the exception of those denoted above as **not medically necessary**).**

Based on review of available data, the Company considers the use of tofacitinib (Xeljanz) for indications other than those listed above to be **investigational.***

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When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of tofacitinib (Xeljanz) in the absence of a treatment failure with adalimumab (Humira) AND etanercept (Enbrel) after at least two months of therapy with each product to be **not medically necessary.****

Background/Overview

Xeljanz is an inhibitor of Janus kinases (JAKs) and is the first inhibitor of the JAKs pathway approved for adults with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate. Janus kinases 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. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Xeljanz modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. Janus kinase enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). Xeljanz inhibited the in vitro activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC50 of 406, 56, and 1377 nM, respectively. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known.

Xeljanz is provided as 5mg tablets. It may be used either as monotherapy or in combination with methotrexate or other non biologic DMARDs. Xeljanz should not be used in combination with biologic DMARDs or immunosuppressants such as azathioprine and cyclosporine. The dose of Xeljanz is 5mg by mouth twice daily with or without food. Dosage interruption is recommended for lymphopenia, neutropenia, and anemia. Xeljanz dosage should be reduced to 5mg once daily in patients with moderate or severe renal insufficiency, moderate hepatic impairment, patients receiving potent inhibitors of CYP 3A4, and patients receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19.

Rheumatoid Arthritis
Rheumatoid Arthritis is a chronic (long-term) disease that causes inflammation of the joints and surrounding tissues. It can also affect other organs. It is considered an autoimmune disease. In an autoimmune disease, the immune system confuses healthy tissue for foreign substances.

Disease-Modifying Anti-Rheumatic Drugs
Disease-modifying anti-rheumatic drugs are used for the treatment of RA, ankylosing spondylitis, psoriatic arthritis and lupus. These drugs slow the disease process by modifying the immune system.

- Methotrexate
- Cyclosporine
- Sulfasalazine
- Mercaptopurine
- Gold Compounds

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Xeljanz was approved in November of 2012 by the FDA for the treatment of moderately to severely active RA in adult patients who have had an inadequate response to or an intolerance to methotrexate. Xeljanz does have a REMS (Risk Evaluation and Mitigation Strategy) program associated with it in order to help educate health care professionals regarding the known or potential serious risks that are associated with the use of Xeljanz. These risks include serious and other important infections, malignancies and other lymphoproliferative disorders, and changes in laboratory parameters. Xeljanz carries a Boxed Warning for serious infections and malignancies similar to other drugs to treat RA.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Xeljanz was studied in five pivotal trials. The trials varied in length from 6-24 months and the number of participants in the five trials varied from 399 subjects to nearly 800 subjects. All participants had moderate to severe RA. Varying by trial, participants had failed therapy with non-biologic or biologic DMARDs. In all trials, patients received either Xeljanz 5mg by mouth twice daily or Xeljanz 10mg by mouth twice daily. Xeljanz was studied as either monotherapy or in combination with non-biologic DMARDs such as methotrexate, depending on the trial. The comparator groups varied by trial but included placebo, placebo plus methotrexate, and adalimumab (Humira). In all trials, Xeljanz had a statistically significant greater number of subjects that achieved American College of Rheumatology (ACR20) response rates versus placebo. However, other outcome measures such as the Health Assessment Questionnaire Disability Index (HAQ-DI) and the Disease Activity Score (DAS28-4[ESR]) varied as to whether Xeljanz showed a statistically significant difference throughout the various trials.

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Policy History

Original Effective Date: 05/22/2013
Current Effective Date: 01/01/2014
05/02/2013 Medical Policy Committee review
05/22/2013 Medical Policy Implementation Committee approval. New policy.
10/10/2013 Medical Policy Committee review
10/16/2013 Medical Policy Implementation Committee approval. Added criteria that requires Humira AND Enbrel prior to use of Xeljanz for rheumatoid arthritis. Created a not medically necessary section to reflect changes.
Next Scheduled Review Date: 10/2014

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.