Xeljanz XR (Tofacitinib) First Once-Daily Oral JAK Inhibitor Approved for Patients with Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that affects more than 1.3 million adults in the United States. The symptoms of RA include pain, stiffness, swelling, and limited motion and function of many joints, particularly small joints in the hands and feet. The diagnosis of RA is made on the basis of the symptoms; the physical examination results; and blood tests that show the presence of anemia, rheumatoid factor, antibodies to cyclic citrullinated peptides, and an elevated erythrocyte sedimentation rate. Although the etiology of RA is unknown, the disease is associated with genetic factors and environmental exposures. The risk factors for RA include smoking, use of reproductive hormones, dietary factors, exposure to microbes, and human leukocyte antigen class II genotypes.

The treatment of patients with RA is based on symptoms and often requires a combination of drugs. Typically, therapy begins with a disease-modifying antirheumatic drug (DMARD), such as methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine. DMARDs are administered concomitantly with nonsteroidal anti-inflammatory drugs and/or low-dose corticosteroids to reduce any swelling, pain, and fever.

For patients with severe RA, the treatment includes biologic agents, which can include DMARDs, that target specific aspects of the immune system, such as anti-tumor necrosis factor (TNF) and interleukin-6.

FDA Approves Xeljanz XR Once-Daily JAK Inhibitor

On February 24, 2016, the US Food and Drug Administration (FDA) approved a new formulation for tofacitinib citrate (Xeljanz XR; Pfizer) as extended-release tablets administered orally once daily. This is the first formulation of a Janus kinase (JAK) inhibitor approved by the FDA for once-daily oral administration. The original formulation of tofacitinib (Xeljanz), which requires twice-daily dosing, was first approved in 2012 for adults with moderate-to-severe active RA who have an inadequate response to or do not tolerate methotrexate. The extended-release formulation reflects the value of once-daily dosing for patient adherence and targets the same patient population. The new formulation of tofacitinib is the first once-daily oral JAK inhibitor approved for patients with RA.

“The availability of Xeljanz XR provides physicians with a new treatment option for people with RA who may prefer an oral once-daily treatment,” said Roy Fleischmann, MD, Clinical Professor, Department of Internal Medicine, the University of Texas Southwestern Medical Center, and Co-Medical Director, Metroplex Clinical Research Center.

Mechanism of Action

Tofacitinib inhibits JAKs, which are intracellular enzymes that transmit signals that arise from cytokine and growth factor receptor interactions on cell membranes. These signals influence hematopoiesis and immune-cell function. Specifically, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which can affect gene expression. By inhibiting JAKs, tofacitinib prevents the phosphorylation and activation of STATs.

Dosing and Administration

Tofacitinib may be used as monotherapy or in combination with methotrexate or with other nonbiologic DMARDs. The recommended dosage of tofacitinib extended-release tablets is 11 mg once daily. The recommended dosage of tofacitinib is 5 mg twice daily.

Patients can switch from tofacitinib 5 mg twice daily to extended-release tofacitinib 11 mg once daily the day after the last dose of tofacitinib 5 mg.

Tofacitinib extended-release tablets should be swallowed whole and should not be crushed, split, or chewed.

Clinical Trials

The safety and effectiveness of tofacitinib are based on clinical trials with tofacitinib 5 mg twice daily, which were evaluated in 7 clinical trials—2 dose-ranging clinical trials and 5 confirmatory clinical trials—in adults with moderately or severely active RA who had an inadequate response to methotrexate.

The primary end points in the confirmatory trials included the proportion of patients who achieved an American College of Rheumatology (ACR) 20 response, the proportion of patients who achieved an ACR70 re-
response, change from baseline in van der Heijde modified Total Sharp Score, changes in Health Assessment Questionnaire-Disability Index, and rates of a 28-joint Disease Activity Score (DAS28)-4 erythrocyte sedimentation rate <2.6.4 In these clinical trials, patients who received tofacitinib with or without a DMARD obtained improvements in clinical response and physical functioning compared with patients who received placebo (with or without a DMARD).4

Two of the confirmatory studies also evaluated the effect of tofacitinib on joint damage and radiographic progression. In one of the studies, tofacitinib monotherapy inhibited the progression of structural damage compared with methotrexate at 6 and 12 months.4 In patients who received methotrexate, 55% had no radiographic progression at 6 months compared with 73% of patients who received tofacitinib 5 mg.4 In the other study, 74% of patients who received placebo and methotrexate had no radiographic progression after 6 months compared with 84% of patients who received tofacitinib 5 mg plus methotrexate.4

Adverse Events

Across the 7 clinical trials of tofacitinib, the most frequently reported adverse reactions during the first 3 months of therapy and occurring in at least 2% of patients who received tofacitinib with or without DMARDs included upper respiratory tract infections, headache, diarrhea, and nasopharyngitis.4 Tofacitinib has no contraindications.4

Drug Interactions

The coadministration of tofacitinib with potent immunosuppressive drugs, including azathioprine, tacrolimus, and cyclosporine, and with biologic DMARDs increases the risk for immunosuppression. As such, tofacitinib should not be combined with biologic DMARDs, including TNF inhibitors, or with potent immunosuppressive drugs.4

Warnings and Precautions

The prescribing information for tofacitinib includes a box warning stating that treatment with tofacitinib is associated with serious infections and with malignancy.4 Serious and sometimes fatal infections have been reported in patients with RA who received tofacitinib. Tofacitinib is not recommended in patients with an active serious infection. Patients should be evaluated and tested for latent or active infection and screened for viral hepatitis before starting tofacitinib therapy.4

In the 7 controlled clinical trials, 11 solid cancers and 1 case of lymphoma were diagnosed among 3328 patients who received tofacitinib with or without a DMARD. Lymphomas and solid cancers have also been observed in long-term extension studies of patients with RA.4 Tofacitinib should be used with caution in patients who are at an increased risk for gastrointestinal (GI) perforation.4 Treatment with tofacitinib has been associated with lymphocyte count abnormalities, neutropenia, anemia, and elevations in liver enzyme and lipid levels.4 Live vaccines should not be used concurrently with tofacitinib.4 Use caution in patients with severe GI narrowing. Symptoms of GI obstruction have occurred after ingestion of other drugs that use a nondeformable extended-release formulation.4

Use in Specific Populations

Tofacitinib should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. It is not known whether tofacitinib is excreted in human milk.4 Because many drugs are excreted in human milk, patients should decide whether to discontinue nursing or discontinue tofacitinib therapy.4 Because the risk for infection is increased in the elderly population and in patients with diabetes, caution is needed when using tofacitinib in these populations.4 The use of tofacitinib in patients with severe hepatic impairment is not recommended. In patients with moderate or severe renal impairment, the recommended dosage of tofacitinib is 5 mg once daily.4

Conclusion

Tofacitinib offers an oral alternative to biologic DMARDs for adults with moderately to severely active RA who have had a poor response to methotrexate. The new formulation of extended-release tofacitinib tablets offers patients the convenience of once-daily dosing compared with the original formulation of twice-daily dosing of tofacitinib, which may have the potential to enhance patient adherence and improve clinical outcomes.

References