

# Pharmaceutical Approval Update

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## Tofacitinib (Xeljanz) Tablets

**Manufacturer:** Pfizer, Madison, N.J.

**Indication:** Tofacitinib is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adults who have had an inadequate response to, or who are intolerant of, methotrexate.

**Drug Class:** Tofacitinib is an oral selective Janus kinase (JAK) inhibitor. It can be taken alone or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs), but it should not be used with biologic drugs, azathioprine (Azasan, Salix), or cyclosporine.

**Uniqueness of Drug:** Tofacitinib interrupts the signaling of several cytokines involved in the immune response.

**Boxed Warning:** Because of the risk of serious infections, lymphomas, and other cancers associated with tofacitinib, the drug was approved with a Risk Evaluation and Mitigation Strategy (REMS) and a patient medication guide. Patients should be tested for latent tuberculosis (TB) before they start tofacitinib therapy. Patients who test positive for latent TB should be treated for the infection before initiating therapy with tofacitinib. All patients, including those who initially tested negative for latent TB, should be monitored for active TB during treatment with this medication.

Cellulitis, herpes zoster, and urinary tract infections have been reported with treatment. Esophageal candidiasis, pneumocystosis, cytomegalovirus infection, and other opportunistic infections have also occurred in association with tofacitinib.

**Warnings and Precautions:** Adverse events in clinical trials of tofacitinib have included upper respiratory tract infections, pharyngitis, headache, diarrhea, and nasopharyngeal inflammation. Tofacitinib carries a risk of serious infections, including TB. Patients who acquire an illness during therapy may need to be hospitalized for clinical tests.

Tofacitinib has also been associated with elevated cholesterol levels, elevated liver enzymes, decreased blood counts, and an increased risk of some cancers.

**Dosage and Administration:** Tofacitinib can be taken with or without food. For patients with RA, tofacitinib may be used as monotherapy or may be combined with methotrexate or other nonbiologic DMARDs. The recommended dose of tofacitinib is 5 mg twice daily. Dose interruption is recommended if lymphopenia, neutropenia, or anemia occurs during treatment.

The dosage should be reduced to 5 mg once daily in patients with moderate or severe renal insufficiency and moderate hepatic impairment; in those receiving potent inhibitors of cytochrome P450 isoenzyme 3A4 (CYP3A4) such as ketoconazole (Nizoral, PriCara/Janssen); and in those receiving one or more concomitant medications that result in moderate

inhibition of CYP3A4 and potent inhibition of CYP2C19, such as fluconazole (Diflucan, Pfizer).

Tofacitinib should not be used in patients with severe hepatic impairment, a lymphocyte count below 500 cells/mm<sup>3</sup>, an absolute neutrophil count below 1,000 cells/mm<sup>3</sup>, or a hemoglobin level below 9 g/dL.

Coadministration of the drug with potent inducers of CYP3A4 (e.g., rifampin) may result in a loss of clinical response or a reduced response to tofacitinib. Live vaccines should not be given concurrently with tofacitinib.

**Commentary:** RA is an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue, leading to inflammation of the joints and surrounding tissues. Taken twice daily, tofacitinib blocks molecules called Janus kinases, which play a role in joint inflammation.

The FDA approved tofacitinib for the treatment of moderate-to-severe RA in patients who cannot take methotrexate or who have not responded to it.

Tofacitinib is intended to slow the progression of the disease. It is the first RA treatment from a new class of pain medications called JAK inhibitors, which interfere with enzymes that contribute to tissue inflammation.

Tofacitinib tablets can be taken alone or with methotrexate and other DMARDs, but they should not be used with biologic DMARDs or with potent immunosuppressive drugs.

**Sources:** [www.xeljanz.com](http://www.xeljanz.com); <http://labeling.pfizer.com/ShowLabeling.aspx?id=959>; <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=81354>

## Perampanel (Fycompa) Tablets

**Manufacturer:** Eisai, Inc., Woodcliff Lake, N.J.

**Indication:** Perampanel is used as an adjunctive therapy for the treatment of partial-onset seizures, with or without secondarily generalized seizures, in patients 12 years of age and older.

**Drug Class:** The compound is described chemically as 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate (4:3). The drug's molecular weight is 362.90 (3/4 hydrate).

**Uniqueness of Drug:** Perampanel is a noncompetitive antagonist of the ionotropic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on postsynaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS) and is implicated in several neurological disorders caused by neuronal overexcitation. The mechanism by which perampanel exerts its antiepileptic effects in humans has not been fully elucidated.

**Boxed Warning.** Aggression, hostility, irritability, anger, homicidal ideation, and threatening behavior have been reported in patients taking perampanel. These reactions occurred in patients with and without a psychiatric history, prior to the aggressive behavior, or with the concomitant use of medications associated with hostility and aggression. Patients and caregivers are advised to contact a health care provider immediately if any of these reactions or atypical changes in mood, behavior,



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or personality are observed during or after perampanel therapy.

Patients should be closely monitored, particularly during the titration period and when they are taking higher doses. The dose should be reduced if behavioral symptoms occur. Therapy should be discontinued immediately if symptoms become severe.

### Warnings and Precautions:

**Serious psychiatric and behavioral reactions.** In the placebo-controlled phase 3 clinical trials, adverse reactions related to hostility and aggression occurred in 12% and 20% of patients receiving perampanel at doses of 8 mg/day and 12 mg/day, respectively, compared with 6% of placebo patients. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. Perampanel-treated patients experienced more adverse reactions of hostility and aggression that led to dose reductions and interruption and discontinuation of therapy more frequently compared with placebo-treated patients.

Neuropsychiatric events (irritability, anger, and anxiety) were reported twice as often with perampanel as with placebo. Other events noted with perampanel more often than with placebo included belligerence, labile affect, agitation, and physical assault. Some of these events were considered serious and life-threatening. Three out of 4,368 perampanel-treated patients exhibited homicidal ideation or made threats in controlled and open-label studies, including non-epilepsy studies.

Patients, their caregivers, and families should be informed that perampanel may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least 1 month after the last dose of perampanel, especially when higher doses are taken and during the initial titration period or at other times of dose increases. The dose should be reduced if symptoms occur. Perampanel should be permanently discontinued if persistent severe or worsening psychiatric symptoms or behaviors occur, and the patient should be referred for psychiatric evaluation.

**Suicidal behavior and ideation.** Antiepileptic agents, including perampanel, may increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. Health care practitioners considering prescribing perampanel or any other antiepileptic drug must balance the risk of suicidal thoughts or behavior with the risk of untreated illness.

**Neurological effects.** Perampanel may cause dose-related adverse events such as dizziness and disturbances in gait or coordination as well as dose-dependent increases in somnolence, fatigue, and lethargy. Prescribers should advise patients not to engage in possibly hazardous activities that call for mental alertness, such as operating motor vehicles or dangerous machinery until the effect of perampanel is known. An increased risk of falls, in some cases leading to head injuries and bone fractures, was also noted with perampanel.

**Withdrawal of antiepileptic drugs.** There is the potential of increased seizure frequency in patients with seizure disorders when antiepileptic drugs are withdrawn abruptly. Perampanel has a half-life of approximately 105 hours. Therefore, even

after abrupt cessation of treatment, blood levels fall gradually.

**Dosage and Administration:** The starting dose of perampanel is 2 mg once daily at bedtime in patients who are not taking enzyme-inducing antiepileptic drugs and 4 mg in patients taking enzyme-inducing antiepileptic agents. The dose may be increased, based on the patient's clinical response and tolerability, by a maximum of 2 mg once daily at bedtime in weekly increments to a dose of 4 mg to 12 mg once daily at bedtime. Dose increases should occur no more frequently than at weekly intervals.

The maximum recommended daily dose is 12 mg once daily at bedtime. For elderly patients, the maximum frequency for dosage increases is every 2 weeks.

**Hepatic impairment.** Based on higher exposure and the longer half-life of perampanel in patients with mild and moderate hepatic impairment, dosage adjustments are recommended. The starting dose should be 2 mg/day, with weekly increments of 2 mg/day every 2 weeks until the target dose is achieved. The maximum recommended daily dose is 6 mg for patients with mild hepatic impairment and 4 mg for patients with moderate hepatic impairment. Dose increases in patients with mild and moderate hepatic impairment, as with all patients, should be based on clinical response and tolerability. Perampanel is not recommended for patients with severe hepatic impairment.

**Renal impairment.** With close monitoring, perampanel can be used in patients with moderate renal impairment. Slower titration may be considered, depending on the patient's clinical response and tolerability. This medication is not recommended for patients with severe renal impairment or in patients undergoing hemodialysis.

**Commentary:** Perampanel's effectiveness was confirmed in three trials in which it was used as once-daily add-on treatment for partial-onset seizures in adults and adolescents. A clinically meaningful reduction in seizure frequency was noted as early as the second week, when a daily dose of 4 mg was achieved.

Perampanel, a glutamate receptor antagonist, is not approved for use in younger patients, but pediatric studies are under way. In three double-blind, placebo-controlled studies involving adolescents, results were similar to those seen in adults.

The FDA's approval of perampanel tablets may offer patients a new approach toward seizure control. A patient medication guide is required to be dispensed.

**Sources:** [www.fda.gov](http://www.fda.gov); <http://us.eisai.com>; <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=81828>

### Teriflunomide (Aubagio) Tablets

**Manufacturer:** Genzyme/Sanofi, Cambridge, Mass.

**Indication:** Teriflunomide is indicated for the treatment of relapsing forms of multiple sclerosis (MS).

**Drug Class:** Teriflunomide is an oral *de novo* pyrimidine synthesis inhibitor of a mitochondrial enzyme called dihydro-orotate dehydrogenase (DHO-DH). The drug's chemical name is (*Z*)-2-cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethylphenyl)-amide. The molecular weight is 270.21.

**Uniqueness of Drug:** As an immunomodulatory agent with anti-inflammatory properties, teriflunomide inhibits DHO-DH, an enzyme involved in pyrimidine synthesis. The mechanism by which teriflunomide exerts its therapeutic effect in MS is unknown, but the medication appears to reduce the number

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of activated lymphocytes in the CNS.

### **Boxed Warning:**

**Hepatotoxicity.** Severe liver injury, including fatal liver failure, has been reported in patients receiving leflunomide (Arava, Sanofi), which is indicated for rheumatoid arthritis (RA). A similar risk would be expected for teriflunomide.

The concomitant use of teriflunomide with other potentially hepatotoxic drugs may increase the risk of severe liver injury. Transaminase and bilirubin levels should be obtained within 6 months before teriflunomide therapy begins. Serum alanine transaminase (ALT) levels should be monitored at least monthly for 6 months after teriflunomide therapy starts.

If drug-induced liver injury is suspected, teriflunomide should be discontinued and an accelerated elimination procedure should be initiated with cholestyramine or charcoal, as described in the section on clearance below.

Teriflunomide is contraindicated in patients with severe hepatic impairment. Patients with pre-existing liver disease may be at an increased risk for the development of elevated serum transaminases when taking teriflunomide.

**Risk of teratogenicity.** Animal data indicate that teriflunomide may cause major birth defects if it is used during pregnancy. Pregnancy must be excluded before teriflunomide therapy is started. Teriflunomide is contraindicated in pregnant women and in women of childbearing age who are not using reliable contraception. Pregnancy must be avoided during teriflunomide treatment or before the completion of an accelerated elimination procedure after teriflunomide treatment.

### **Warnings and Precautions:**

**Hepatotoxicity.** Severe liver injury, including fatal liver failure and dysfunction, has been reported in some patients who were treated with leflunomide (Arava). A similar risk is expected for teriflunomide. Patients with pre-existing liver disease may be at an increased risk of elevated serum transaminases during therapy. In general, patients with pre-existing acute or chronic liver disease and those with serum ALT levels above two times the upper limit of normal before treatment should not use teriflunomide. Teriflunomide is contraindicated in patients with severe hepatic impairment.

Transaminases and bilirubin levels should be determined within 6 months before the initiation of teriflunomide therapy. ALT levels should be monitored at least monthly for 6 months after teriflunomide treatment is started.

**Pregnancy.** Teriflunomide has not been evaluated adequately in pregnant women; however, based on animal studies, teriflunomide may increase the risk of teratogenic effects when administered during pregnancy. Women of childbearing age should not begin taking teriflunomide until pregnancy is ruled out and until contraception has been confirmed as being reliable. Before starting treatment, patients must be fully counseled on the potential for serious risk to the fetus.

**Accelerating drug clearance.** Teriflunomide is eliminated slowly from plasma. Without an accelerated elimination procedure, it takes 8 months, on average, to reach plasma concentrations of less than 0.02 mg/L, and because of individual variations in drug clearance, it may take as long as 2 years. An accelerated elimination procedure may be used at any time after teriflunomide is discontinued.

Cholestyramine 8 g is administered every 8 hours for 11

days. If a dose of 8 g three times daily is not well tolerated, cholestyramine 4 g three times daily may be used. Alternatively, 50 g oral activated charcoal powder may be taken every 12 hours for 11 days.

**Effects on bone marrow, immunosuppression, and infections.** Mean decreases in the white blood cell (WBC) count of approximately 15% and in the platelet count of approximately 10% were observed in placebo-controlled trials with teriflunomide 7 mg and 14 mg. The decrease in mean WBC count occurred during the first 6 weeks, and the WBC count remained low during treatment. In placebo-controlled studies, neutrophil counts below  $1.5 \times 10^9/L$  were observed in 10% and 15% of patients receiving teriflunomide 7 mg and 14 mg, respectively, compared with 5% of patients receiving placebo. Lymphocyte counts below  $0.8 \times 10^9/L$  were noted in 7% and 10% of patients receiving teriflunomide 7 mg and 14 mg, respectively, compared with 5% of patients receiving placebo.

Patients with an active acute or a chronic infection should not start treatment until the infectious organism has been eradicated. If a serious infection develops, the practitioner should consider suspending treatment and using an accelerated elimination procedure. The benefits and risks of treatment should be assessed before treatment resumes. Patients in treatment should be instructed to report symptoms of an infection to their health care professional.

Teriflunomide is not recommended for patients with severe immunodeficiency; bone marrow disease; or severe, uncontrolled infections. Medications like teriflunomide have the potential to lead to immunosuppression and may cause patients to be more susceptible to infections.

**Vaccination.** No clinical data are available regarding the efficacy and safety of vaccinations in patients taking teriflunomide; however, live vaccines are not recommended. Clinicians should consider the drug's long half-life when contemplating the administration of a live vaccine after stopping teriflunomide.

**Malignancy.** The risk of malignancy, particularly a lymphoproliferative disorder, is increased with the use of some immunosuppressive agents. There is a potential for immunosuppression with teriflunomide.

**Peripheral neuropathy.** In clinical studies, polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome) were reported more frequently with the study drug than with placebo.

**Acute renal failure.** In clinical trials, 10 of 844 (1.2%) teriflunomide-treated subjects had transient acute renal failure. Creatinine values were increased by 100% or more from baseline, compared with no increases for the 421 placebo subjects.

Teriflunomide caused increases in renal uric acid clearance, with mean decreases of 20% to 30% in serum uric acid. Acute uric acid nephropathy is a probable explanation for the transient acute renal failure seen with teriflunomide.

**Hyperkalemia.** In placebo-controlled trials, treatment-emergent hyperkalemia exceeding 7.0 mmol/L occurred in eight of 829 (1.0%) teriflunomide-treated subjects, compared with 1 in 414 (0.2%) placebo-treated subjects. Two teriflunomide-treated subjects had potassium levels that exceeded 7.0 mmol/L, and they also had acute renal failure. Serum potassium levels should be checked in teriflunomide-treated patients who have symptoms of hyperkalemia or acute renal failure.

**Skin reactions.** Rare cases of Stevens–Johnson syndrome

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and toxic epidermal necrolysis have been reported in patients with RA who received leflunomide. A similar risk is likely with teriflunomide.

**Hypertension.** In placebo-controlled studies, the mean change from baseline in systolic blood pressure was 2.9 mm Hg and 2.7 mm Hg for teriflunomide 7 mg and 14 mg, respectively. Systolic blood pressure was reduced by 1.3 mm Hg with placebo.

**Respiratory effects.** During treatment with leflunomide, interstitial lung disease and worsening of pre-existing interstitial lung disease were reported. A similar risk is expected for teriflunomide.

**Use with other immunosuppressives or immunomodulators.** Coadministration with antineoplastic or immunosuppressive therapies used in MS has not been evaluated. Safety studies in which teriflunomide was given with other immunomodulating therapies for up to 1 year, such as interferon beta and glatiramer acetate injection (Copaxone, Teva), did not signal any safety concerns. The long-term safety of these combinations in MS has not been established.

If the patient is switched from teriflunomide to another agent with a potential for hematological suppression, it would be prudent to monitor for hematological toxicity; there is overlap of systemic exposure to both compounds.

**Dosage and Administration:** The recommended dose of teriflunomide is 7 mg or 14 mg orally once daily with or without food.

Transaminase and bilirubin levels should be obtained within 6 months before the initiation of teriflunomide. ALT levels should be monitored at least monthly for 6 months after teriflunomide therapy is initiated. A complete blood cell count (CBC) should be obtained within 6 months before teriflunomide treatment begins. Further monitoring should be based on signs and symptoms of infection.

Before therapy begins, patients should be screened for latent TB infection with a tuberculin skin test. Blood pressure should also be measured before treatment starts and periodically thereafter.

**Commentary:** MS is a chronic, inflammatory CNS autoimmune disease that disrupts communication between the brain and other parts of the body. For most patients with MS, relapses are initially followed by remissions. Over time, recovery periods may be incomplete, leading to progressive decline.

Teriflunomide is an immunomodulator with anti-inflammatory properties and may cause a reduced number of activated lymphocytes in the CNS. The drug's approval was based on phase 3 data from the Teriflunomide Multiple Sclerosis Oral (TEMSO) trial. In the trial, teriflunomide 14-mg tablets significantly reduced the annualized relapse rate and the time to disability progression at 2 years versus placebo in patients with relapsing MS. The 7-mg dose resulted in a significantly reduced annualized relapse rate.

The labeling for teriflunomide tablets calls for a patient medication guide to be dispensed with the prescription.

Many patients with MS struggle with the additional burden of injectable therapies administered daily to weekly. The FDA's approval of teriflunomide is an encouraging advancement.

**Sources:** [www.aubagio.com](http://www.aubagio.com); [www.nationalmssociety.org](http://www.nationalmssociety.org); <http://products.sanofi.us/aubagio/aubagio.pdf> ■