Mulpela (lusutrombopag) tablets

Manufacturer: Shionogi Inc., Florham Park, NJ
Date of Approval: July 31, 2018

Indication: Lusutrombopag is indicated for thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a medical or dental procedure.

Drug Class: An oral thrombopoietin (TPO) receptor agonist

Uniqueness of Drug: Lusutrombopag is the second oral TPO receptor agonist to garner FDA approval for adults with chronic liver disease who are scheduled to undergo a procedure; the drug was also granted priority review and fast track designation.

Contraindications: None

Warnings and Precautions:

Thrombotic/thromboembolic complications. TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Patients should have their platelet counts monitored and should also be monitored for the appearance of thromboembolic events. If a thromboembolic event occurs, treatment of the event should begin promptly. Portal vein thrombosis (PVT) has been reported in patients with chronic liver disease treated with TPO receptor agonists. In lusutrombopag-treated patients in clinical trials, PVT was reported in 1% (2 of 171) of patients, as well as 1% (2 of 170) of placebo-treated patients. PVT was identified post-procedure in protocol-specified imaging. The thromboses were not associated with a substantial platelet-count increase. Increased thrombotic risk should be considered when administering lusutrombopag to patients with known risk factors for thromboembolism, such as those with genetic pro-thrombotic conditions (e.g., Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency, or Protein C or S deficiency). In patients with ongoing or prior thrombosis or absence of hepatopetal blood flow, lusutrombopag should only be used if the potential benefit justifies the potential risk. The drug should not be given to patients with chronic liver disease to normalize platelet counts.

Use in Specific Populations: The risks of using lusutrombopag in breastfeeding or pregnant women are not known. The drug has not been studied in pediatric or geriatric patients. Lusutrombopag’s pharmacokinetics have not been studied in individuals with renal or hepatic dysfunction.

Dosage and Administration: Dosing should begin 8 to 14 days prior to a scheduled procedure. Patients should undergo their procedure two to eight days after the last dose. The recommended lusutrombopag dose is 3 mg taken orally once daily with or without food for seven days. In the case of a missed dose, patients should take the missed dose as soon as possible on the same day and return to the normal schedule the following day. Lusutrombopag has only been investigated as a single, seven-day, once-daily dosing regimen in clinical trials in patients with chronic liver disease.

Commentary: Lusutrombopag’s approval was based on two randomized, double-blind, placebo-controlled trials, L-PLUS 1 and L-PLUS 2, in patients (n = 312) with chronic liver disease and severe thrombocytopenia who were undergoing an invasive procedure and had a platelet count below 50 x 10^9/L. Patients were randomized in a 1:1 manner to receive lusutrombopag 3 mg or placebo once daily for up to seven days. Seventy-eight percent (38/49) of patients in L-PLUS 1 required no platelet transfusion prior to the primary invasive procedure, compared with 13% (6/48) of placebo-treated patients (P < 0.0001). Sixty-five percent of lusutrombopag-treated patients (70/108) in L-PLUS 2 required no platelet transfusion prior to the primary invasive procedure or rescue therapy for bleeding, compared with 29% (31/107) of placebo-treated patients (P < 0.0001). The most common adverse reaction occurring in clinical trials, in at least three percent of patients, was headache.


Takhzyro (lanadelumab-flyo) injectable

Manufacturer: Dyax Corp, Lexington, MA
Date of Approval: August 23, 2018

Indication: Lanadelumab is indicated for prophylaxis to prevent hereditary angioedema (HAE) attacks in patients aged 12 years and older.

Drug Class: A plasma kallikrein inhibitor monoclonal antibody

Uniqueness of Drug: Lanadelumab, a fully human IgG1 monoclonal antibody, is the first monoclonal antibody approved in the U.S. for the treatment of patients aged 12 years and older with types I and II HAE to prevent the occurrence of swelling attacks. HAE, a rare and serious genetic disease, affects people with low levels of C1 esterase inhibitor (C1-INH) and poorly functioning C1-INH proteins. This results in recurrent and unpredictable episodes of severe swelling in various areas of the body, including the stomach, limbs, face, and throat. HAE affects an estimated one in 50,000 people, and 85% of cases are Type I HAE (the most common type). Symptoms typically begin in childhood and worsen following puberty. Some patients have many attacks each month, while other patients can go months without any attack. The FDA granted this application priority review and breakthrough therapy designations.

Contraindications: None

Warnings and Precautions: Hypersensitivity reactions have occurred. In case of severe hypersensitivity reaction, lanadelumab should be discontinued and appropriate treatment should be started.

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**Drug-laboratory test interactions.** Coagulation tests: Lanadelumab can elevate the activated partial thromboplastin time (aPTT) due to interaction with the aPTT assay. In trials, prolongation of aPTT (> 1 x ULN) was observed at one or more time points in 3 patients treated with 150 mg every 4 weeks, 9 patients treated with 300 mg every 4 weeks, and 11 patients treated with 300 mg every 2 weeks, compared to 5 placebo-treated patients. One patient in the group receiving 300 mg every 2 weeks had a transient aPTT prolongation ≥ 1.5 x ULN, which was confounded by ongoing heparin therapy. No patient with an aPTT increase and who was treated with lanadelumab experienced abnormal bleeding. International normalized ratio (INR) values did not differ between treatment groups.

**Special Populations:** There are no data on pregnant or breastfeeding women.

**Availability, Dosage, Administration:** Lanadelumab has a half-life of approximately two weeks and is administered as one subcutaneous self-injection of 300 mg every two weeks. Dosing every four weeks may be considered in some patients.

**Commentary.** Lanadelumab’s approval was based on data from a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in HAE patients (n = 125). Patients who received the drug had clinically meaningful and statistically significant reductions in the rate of investigator-confirmed HAE attacks compared to placebo-treated patients over a six-month treatment period. In the Phase III HELP (Hereditary Angioedema Long-term Prophylaxis) Study, lanadelumab reduced the number of monthly HAE attacks by about 87% (n = 27) compared to placebo-treated patients (n = 41) when administered at 300 mg every two weeks, and reduced monthly HAE attacks by 73% (n = 29) compared to placebo-treated patients (n = 41) when administered at 300 mg every four weeks (P <0.001). In a 26-week clinical trial (n = 125), patients treated with lanadelumab 300 mg every 2 weeks also had 83% fewer moderate-to-severe attacks, and 87% had fewer attacks requiring on-demand treatment. A prespecified, exploratory analysis showed that 44% of patients (n = 27) receiving lanadelumab 300 mg every two weeks had no attacks compared to placebo-treated patients (2%, n = 41) for the 26-week treatment period from day 0 to 182. In a post-hoc analysis (days 70 to 182), 77% of patients (n = 26) treated with lanadelumab in the same dosage arm of the trial were attack-free compared to placebo-treated patients (3%, n = 37). The most commonly reported adverse reactions occurring in 10% or more of patients, and higher than in placebo-treated patients, were diarrhea; dizziness; headache; injection-site reactions; myalgia; rash; and upper respiratory infection.


**Ajovy (fremanezumab-vfrm) injection**

**Manufacturer:** Teva Pharmaceuticals, Jerusalem, Israel

**Date of Approval:** September 14, 2018

**Indication:** Ajovy (fremanezumab-vfrm) is indicated for the preventive treatment of migraines in adults.

**Drug Class:** Anti-calcitonin gene-related peptide (CGRP) ligand monoclonal antibody

**Uniqueness of Drug:** This is the first subcutaneous injectable, humanized, monoclonal antibody that is also a calcitonin-gene-related peptide (CGRP) antagonist agent for migraine prophylaxis management, available in quarterly (every three months) and monthly dosing options. The drug was given a priority review by the FDA.

**Contraindications:** This agent is contraindicated in patients with serious hypersensitivity to fremanezumab or to any of the excipients in the formulation.

**Warnings and Precautions:**

**Hypersensitivity reactions.** Rash, pruritus, drug hypersensitivity, and urticaria were among the reactions reported in clinical trials. Most reactions were mild to moderate, but some led to discontinuation or required corticosteroid treatment. Most reactions were reported from within hours to one month following drug administration. If a hypersensitivity reaction occurs, the drug should be discontinued and appropriate therapy should be given.

**Availability, Dosage, Administration:** Fremanezumab is available as a 225 mg/1.5 mL single-dose prefilled syringe, and should only be administered via the subcutaneous route. Two subcutaneous dosing options are available: 225 mg monthly, or 675 mg every 3 months, which is administered as three consecutive subcutaneous injections of 225 mg each. When switching dosage options, the first dose of drug in the new regimen should be administered on the next scheduled date of administration. If a dose is missed, it should be administered as soon as possible. Fremanezumab may be administered by health care professionals, patients, and/or caregivers. Prior to use, proper training should be given to patients and/or caregivers on the preparation and administration of the prefilled syringe, including aseptic technique. It should be removed from the refrigerator at least 30 minutes before administration.

**Commentary:** Fremanezumab’s safety and efficacy was evaluated in two phase 3, placebo-controlled clinical trials that enrolled patients with disabling migraine. It was studied as both a monotherapy prophylaxis agent and in combination with oral prophylaxis agents. More than 1,000 patients with chronic migraine were enrolled, and experienced a reduction in monthly migraine days during the 12-week study period. Patients who were randomly assigned to receive 675 mg of active treatment for one month followed by either 225-mg dose treatments for the following two months (“monthly dosing”) or placebo for the next two months (“quarterly dosing”) had a significantly reduced number of monthly headache days (4.6 days and 4.3 days, respectively) compared to placebo-treated patients (2.5 days; P < 0.0001 for both comparisons). Patients (n = 873) with episodic migraine had reduced monthly migraines in both the monthly and quarterly dosing groups (the study’s primary endpoint) compared to placebo-treated patients (3.7 days [monthly dosing], 3.4 days [quarterly dosing], 2.2 days [placebo]; P < 0.0001). The most common adverse reaction (incidence > 5% and greater than placebo) in clinical trials was injection-site reactions.

**Source:** Teva Pharmaceuticals, Ajovy prescribing information.