Burosumab-twza (Crysvita)

**Manufacturer:** Ultragenyx Pharmaceutical, Inc., Novato, California

**Date of Approval:** April 17, 2018

**Indication:** Burosumab is a fibroblast growth factor 23 (FGF23)-blocking antibody indicated for the treatment of x-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

**Drug Class:** Monoclonal antibody (endocrine)

**Uniqueness of Drug:** Burosumab is the first drug approved by the Food and Drug Administration (FDA) to treat XLH, a rare inherited form of rickets. Vitamin D therapy, used to treat other forms of the disease, is not effective in treating XLH, which causes low levels of phosphorus in the blood. It leads to impaired bone growth and development in children and adolescents and problems with bone mineralization throughout a patient’s life. Burosumab was granted FDA breakthrough therapy and orphan drug designations, and Ultragenyx is receiving a rare pediatric disease priority review voucher.

**Warnings and Precautions:**

- **Contraindications.** Burosumab should not be used with oral phosphate and active vitamin D analogues. Do not initiate burosumab treatment if the patient’s serum phosphorus is within or above the normal range for their age.
- **Renal impairment.** Burosumab should not be administered in patients with severe renal impairment or end-stage renal disease because these conditions are associated with abnormal mineral metabolism.
- **Hypersensitivity.** Hypersensitivity reactions (e.g., rash, urticaria) have been reported in patients treated with burosumab. Discontinue its use if serious hypersensitivity reactions occur and initiate appropriate medical treatment.
- **Hyperphosphatemia and risk of nephrocalcinosis.** Increases in serum phosphorus to above the upper limit of normal may be associated with an increased risk of nephrocalcinosis. For patients already taking burosumab, dose interruption and/or reduction may be required based on serum phosphorus levels.

**Injection-site reactions.** Administration of burosumab may result in local injection-site reactions. Discontinue burosumab if severe reactions occur and administer appropriate medical treatment.

**Immunogenicity.** As with all therapeutic proteins, there is potential for immunogenicity; however, the potential clinical impact of antibodies to burosumab is not known.

**Dosage and Administration:** Burosumab is administered by subcutaneous injection by a health care provider. Oral phosphate and active vitamin D analogues should be discontinued one week before the initiation of treatment. The patient’s fasting serum phosphorus concentration should be below the reference range for age prior to initiation of treatment.

**For pediatric patients (1–18 years of age), the recommended starting dose is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg. The recommended dose regimen in adults is 1.0 mg/kg of body weight, rounded to the nearest 10 mg, up to a maximum dose of 90 mg, administered every four weeks.

After initiation of treatment with burosumab, assess fasting serum phosphorus on a monthly basis for the first three months of treatment, and thereafter as appropriate. Dose adjustments should be made based upon patient serum phosphorus levels, but should not be adjusted more frequently than every four weeks. Consult the full prescribing information for specific details.

**Commentary:** The safety and efficacy of burosumab were studied in four clinical trials. In the placebo-controlled trial, 94% of adults receiving burosumab once a month achieved normal phosphorus levels compared with 8% of those receiving placebo. In children, 94% to 100% of patients treated with burosumab every two weeks achieved normal phosphorus levels. In both children and adults, x-ray findings associated with XLH improved with burosumab therapy. Comparison of the results to a natural history cohort also provided support for the effectiveness of burosumab.

The most common adverse reactions in adults taking burosumab were back pain, headache, restless leg syndrome, decreased vitamin D, dizziness, and constipation. The most common adverse reactions in children were headache, injection-site reaction, vomiting, decreased vitamin D, and pyrexia.

**Sources:** FDA, Crysvita prescribing information

Ibalizumab-uiyk (Trogarzo)

**Manufacturer:** TaiMed Biologics USA Corp., Irvine, California

**Date of Approval:** March 6, 2018

**Indication:** Ibalizumab, in combination with other antiretrovirals, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.

**Drug Class:** Antiretroviral agent, CD4-directed post-attachment HIV-1 inhibitor

**Uniqueness of Drug:** Ibalizumab is the first HIV therapy with a novel mechanism of action in more than 10 years. Ibalizumab, a humanized monoclonal antibody, blocks the HIV virus from infecting host cells by binding to extracellular domain 2 of the CD4+ receptor, a site different from other antiretrovirals currently on the market. It is given intravenously (IV) once every 14 days and used in combination with other antiretrovirals. The Food and Drug Administration (FDA) granted the ibalizumab application fast-track, priority review, and breakthrough therapy designations. It also received orphan drug designation.

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Dr. Choy is a freelance medical writer living in New York City.
Warnings and Precautions:

**Immune reconstitution inflammatory syndrome.** Immune reconstitution inflammatory syndrome was reported in one patient treated with ibalizumab in combination with other antiretrovirals. During the initial phase of combination therapies, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment.

**Dosage and Administration:** IV ibalizumab is administered by a trained medical professional as a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every two weeks after dilution in 250 mL of 0.9% sodium chloride injection, USP.

Ibalizumab is given as an IV infusion in the cephalic vein of the patient’s right or left arm. If this vein is not accessible, an appropriate vein located elsewhere can be used. Do not administer ibalizumab as an IV push or bolus.

The duration of the first infusion (loading dose) should be no less than 30 minutes. If no infusion-associated adverse reactions have occurred, the duration of the subsequent infusions (maintenance doses) can be decreased to no less than 15 minutes.

After the infusion is complete, flush with 30 mL of 0.9% sodium chloride injection, USP.

All patients must be observed for one hour after completion of ibalizumab administration for at least the first infusion. If the patient does not experience an infusion-associated adverse reaction, the post-infusion observation time can be reduced to 15 minutes thereafter.

If a maintenance dose (800 mg) is missed by three days or longer beyond the scheduled dosing day, a loading dose (2,000 mg) should be administered as early as possible. Resume maintenance dosing (800 mg) every 14 days thereafter.

**Commentary:** The FDA approval of ibalizumab was based on a phase 3 trial of 40 multidrug-resistant HIV-1 patients, of whom 33 (82.5%) achieved the primary endpoint of a viral load reduction of at least 70% following a seven-day treatment period. At the end of the trial (24 weeks of treatment), the viral load was undetectable in 43% of study participants.

The most common adverse reactions (all grades) reported in at least 5% of patients during clinical trials were diarrhea, dizziness, nausea, and rash. Most (90%) of the reactions reported were mild or moderate in severity.

**Sources:** TaiMed Biologics, Trogarzo prescribing information

**Tildrakizumab-asnm (Ilumya)**

**Manufacturer:** Sun Pharmaceuticals Ltd., Princeton, New Jersey

**Date of Approval:** March 21, 2018

**Indication:** Tildrakizumab is an interleukin (IL)-23 antagonist indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

**Drug Class:** Interleukin inhibitor

**Uniqueness of Drug:** Tildrakizumab, a humanized immunoglobulin G1 kappa monoclonal antibody, targets IL-23p19 and blocks the interaction of IL-23 with its receptor, thereby inhibiting release of proinflammatory cytokines and chemokines.

**Warnings and Precautions:**

**Hypersensitivity reactions.** Cases of angioedema and urticaria occurred in tildrakizumab-treated patients in clinical trials. If a serious hypersensitivity reaction occurs, discontinue the drug immediately and initiate appropriate therapy.

**Infections.** Tildrakizumab may increase the risk of infection. Treatment with tildrakizumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing tildrakizumab. Instruct patients to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, monitor the patient closely and consider discontinuation of tildrakizumab until the infection resolves.

**Pretreatment evaluation for tuberculosis (TB).** Evaluate patients for TB infection prior to initiating treatment with tildrakizumab. Initiate treatment of latent TB before administering tildrakizumab. Monitor patients for signs and symptoms of active TB during and after tildrakizumab treatment. Consider anti-TB therapy prior to initiation of tildrakizumab in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Do not administer tildrakizumab to patients with active TB infection.

**Immunizations.** Before initiating therapy with tildrakizumab, consider completion of all age-appropriate immunizations according to current immunization guidelines. Avoid the use of live vaccines in patients treated with tildrakizumab. No data are available on the response to live or inactivated vaccines.

**Dosage and Administration:** Tildrakizumab is administered by a health care provider via subcutaneous injection. The recommended dose is 100 mg at weeks 0 and 4, then every 12 weeks thereafter. Each prefilled syringe is for a single dose of 1 mL, which provides 100 mg of tildrakizumab per syringe. If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regularly scheduled interval.

**Commentary:** The Food and Drug Administration’s approval of tildrakizumab for the treatment of moderate-to-severe plaque psoriasis was based on data from the phase 3 reSURFACE clinical development program. The two multicenter, randomized, double-blind, placebo-controlled trials—reSURFACE 1 and reSURFACE 2—involved 926 adults with moderate-to-severe plaque psoriasis; 616 were treated with tildrakizumab-asnm, and 310 received placebo. Both studies met the primary efficacy endpoints, demonstrating significant clinical improvement with tildrakizumab compared with placebo when measured by at least a 75% reduction in Psoriasis Area and Severity Index score and Physician Global Assessment score of “clear” or “minimal” at week 12 after two doses. The most common adverse reactions occurring at an incidence of 1% of greater were upper respiratory infections, injection-site reactions, and diarrhea.

**Sources:** Sun Pharmaceuticals, Ilumya prescribing information