Febuxostat (Uloric)

Manufacturer: Takeda Pharmaceuticals, Inc., North America, Deerfield, Ill.

Indication: Febuxostat is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia (excess uric acid) in patients with gout. This product is not recommended for patients with asymptomatic hyperuricemia.

Drug Class: The chemical formula is 2-[3-cyano-4-isobutoxyphenyl]-4-methylthiazole-5-carboxylic acid; 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid. The molecular weight is 316.37 daltons.

Uniqueness of Drug: Febuxostat is a potent non-purine, selective inhibitor of XO. Uric acid is the final product of purine metabolism. Inhibition of XO helps to reduce uric acid, thus preventing or at least decreasing the frequency of gout attacks.

Febuxostat is potent in inhibiting both oxidized and reduced forms of XO. Unlike febuxostat, allopurinol (e.g., Zyloprim, Faro) does not provide persistent enzyme inhibition and it has weaker hypouricemic activity. Allopurinol is prescribed for the treatment of chronic gout and is used to prevent rather than to treat gout attacks. More importantly, because allopurinol and its metabolites are purine analogues, they also inhibit other enzymes involved in purine and pyrimidine metabolism. In contrast, febuxostat blocks and helps to prevent uric acid production, thereby lowering elevated serum levels.

Warnings and Precautions:

Gout flares. After initiation of febuxostat therapy, an increase in gout flares is frequently observed. This increase is caused by reduced serum uric acid levels, resulting in mobilization of urate from tissue deposits. To prevent gout flares when febuxostat is initiated, concurrent prophylactic treatment with a nonsteroidal anti-inflammatory drug (NSAID) or colchicine is recommended.

Cardiovascular events. In randomized, controlled studies, patients receiving febuxostat had higher rates of cardiovascular thromboembolic events, such as death, nonfatal myocardial infarction (MI), and nonfatal stroke, compared with patients receiving allopurinol. A causal relationship with febuxostat has not been established. Patients should be monitored for signs and symptoms of MI.

Liver enzyme elevations. During randomized, controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed. No dose–effect relationship for these elevations was noted. Laboratory assessment of liver function is recommended at two and four months after initiation of febuxostat and periodically thereafter.

Dosage and Administration: To treat hyperuricemia (defined as a serum uric acid level of 6.8 mg/dL or above) in patients with gout, febuxostat tablets are recommended at a dose of 40 mg or 80 mg once daily. The recommended starting dose is 40 mg once daily. For patients who do not achieve a serum uric acid level below 6 mg/dL after two weeks with 40 mg, the 80-mg dose is recommended. Febuxostat can be taken without regard to food or antacid use.

Special populations. No dose adjustments are necessary for patients with mild-to-moderate renal or hepatic impairment.

Uric acid level. Testing for the target serum uric acid level of less than 6 mg/dL may be performed as early as two weeks after febuxostat therapy is initiated.

Gout flares. Preventing gout flares with an NSAID or colchicine is recommended upon initiation of febuxostat therapy, and prophylaxis may be beneficial for up to six months. If a gout flare occurs during febuxostat treatment, the drug does not need to be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient.

Commentary: Gout is a serious health condition that affects three to five million Americans, and it is increasing in incidence and prevalence. It is characterized by flares of acute arthritis, chronic gouty arthropathy, tophi, and uric acid urolithiasis. Gout is associated with a broad range of comorbidities, including cardiovascular disease, chronic kidney disease, and metabolic syndrome. The underlying metabolic aberration in gout is hyperuricemia, which can develop into gout when urate crystals are formed from supersaturated body fluids and the crystals are deposited in joints, tophi, and parenchymal organs.

Uric acid is an end product that is created when the body breaks down purines. Hyperuricemia is a precursor to gout; the higher the urate level, the greater the risk of gout. Experts recognize that a goal in treating chronic gout is to reduce and maintain serum uric acid levels of below 6 mg/dL. Febuxostat effectively lowers uric acid levels in patients with hyperuricemia associated with gout.

This medication was evaluated in multiple clinical trials involving more than 4,000 subjects, with some studies lasting up to five years. Febuxostat represents the first new treatment option in 40 years for millions of patients.

Sources: www.uloric.com; www.fda.gov

Hylan G-F 20 (Synvisc-One)


Indication: Hylan G-F 20 is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have not responded adequately to conservative nonpharmacological therapy and simple analgesics such as acetaminophen.

Drug Class: This agent is an elastoviscous fluid that contains hylan polymers produced from chicken combs. Hylans are derivatives of hyaluronan (sodium hyaluronate), a natural complex sugar of the glycosaminoglycan family. Hyaluronan is a long-chain polymer that contains repeating disaccharide units of Na-glucuronate-N-acetylgalcosamine.

Uniqueness of Product: This viscosupplementation prod-
uct provides pain relief from a single injection. Hylan G-F 20 may simplify the management of OA knee pain and reduce the overall cost of therapy.

**Warnings:** The concomitant use of disinfectants containing quaternary ammonium salts for skin preparation should be avoided because hyaluronan can precipitate in their presence. Hylan GF-20 should not be injected via an extra-articular route or into the synovial tissues and capsule. Local and systemic adverse events, generally in the area of the injection, have occurred following extra-articular injection. Intravascular injections of this product may cause systemic adverse events.

**Precautions:** The effectiveness of a single treatment cycle, consisting of fewer than three injections of Hylan G-F 20, has not been established. The safety and effectiveness of Hylan G-F 20 in severely inflamed knee joints or in locations other than the knee and for conditions other than OA have not been established. Anesthetics and other drugs should not be injected into the knee joint during Hylan G-F 20 therapy. Such medications can dilute the products and may affect its safety and effectiveness.

Caution is necessary with patients who are allergic to avian proteins, feathers, and egg products. Hylan G-F 20 should be used with caution when there is evidence of lymphatic or venous stasis in a patient’s leg. Strict aseptic administration technique must be followed.

**Dosage and Administration:** Hylan G-F 20 is delivered as three combined doses in one single 6-mL injection. The syringe is intended for a single use. The contents of the syringe must be used immediately after its packaging is opened. Any unused Hylan G-F 20 should be discarded. The product should not be used if the package has been opened or is damaged. This medication should be stored in its original packaging and at room temperature below 86°F (30°C), and it should be protected from light. Hylan G-F 20 should not be frozen. Synovial fluid or effusion should be removed before each injection.

**Commentary:** Hylan G-F 20 is a viscosupplement that lubricates and cushions the knee joint and relieves pain. In knees affected by OA, the joint (synovial) fluid can break down and might not provide needed cushioning. Hylan G-F 20 supplements the knee fluid to relieve pain and to improve the knee joint’s natural shock-absorbing abilities, allowing patients to move more freely for up to six months and resume activities. Hylan G-F 20 is made from a natural substance similar to that found in normal, healthy joint fluid.

**Source:** www.synvischcp.com

**Fibrinogen Concentrate (Human) (RiaSTAP)**

**Manufacturer:** CSL Behring LLC, Kankakee, Ill.

**Indication:** RiaSTAP: an orphan drug, is indicated for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. It is not indicated for dysfibrinogenemia.

**Drug Class:** Fibrinogen (factor I) is a soluble plasma glycoprotein with a molecular weight of about 340 kilodaltons (kd). The native molecule is a dimer and consists of three pairs of polypeptide chains (αα, Bβ, and γ). Fibrinogen is a physiological substrate of three enzymes: thrombin, factor XIIIa, and plasmin.

During coagulation, thrombin cleaves the αα and Bβ chains, releasing fibrinopeptide A (FPA) and fibrinopeptide B (FPB). FPA is separated rapidly, and the remaining molecule is a soluble fibrin monomer (fibrin I). The slower removal of FPB results in formation of fibrin II that is capable of polymerization occurring by aggregation of fibrin monomers. The resulting fibrin is stabilized in the presence of calcium ions and by activated factor XIII, which acts as a transglutaminase. Factor XIIIa-induced cross-linking of fibrin polymers renders the fibrin clot more elastic and more resistant to fibrinolysis. Cross-linked fibrin is the final result of the coagulation cascade, providing tensile strength to a primary hemostatic platelet plug and structure to the vessel wall.

**Uniqueness of Drug:** RiaSTAP is a heat-treated, lyophilized fibrinogen (coagulation factor I) powder made from pooled human plasma. Each vial contains 900 to 1,300 mg of fibrinogen, 400 to 700 mg of human albumin, 375 to 660 mg of L-arginine HCl, 200 to 350 mg of sodium chloride, and 50 to 100 mg of sodium citrate. Sodium hydroxide and hydrochloric acid may have been used to adjust the pH.

All plasma used in the manufacture of this agent is tested with FDA-licensed serological assays for hepatitis B surface antigen and antibodies to human immunodeficiency virus–1 (HIV-1), HIV-2, and hepatitis C virus (HCV). Plasma that is assessed by FDA-licensed Nucleic Acid Testing (NAT) for HCV and HIV-1 is nonreactive, or negative.

For HBV, an investigational NAT procedure is used, although the significance of a negative result has not been established. The plasma is also tested by NAT for hepatitis A virus (HAV) and B19 virus (B19V). Only plasma that has passed virus screening is used for production, and the limit for B19V in the fractionation pool is set not to exceed 104 IU/mL of B19V DNA.

The fibrinogen concentrate is made from cryoprecipitate into a glycine precipitate, which is then further purified by several precipitation and adsorption steps. The manufacturing process reduces the risk of virus transmission in several phases, consisting of cryoprecipitation, aluminum hydroxide (Al(OH)₃) adsorption/glycine precipitation/Al(OH)₃ adsorption, heat treatment (+60°C for 20 hours in an aqueous solution), and two subsequent glycine precipitation steps. These steps are validated in a series of in vitro experiments for their capacity to inactivate and remove both enveloped and nonenveloped viruses.

**Warnings and Precautions:**

**Allergic reactions:** If patients have symptoms of an allergic or an early hypersensitivity reaction (hives, generalized urticaria, tightness of the chest, wheezing, hypotension, or anaphylaxis), administration of RiaSTAP should be stopped immediately. Treatment of the reaction is given according to its nature and severity.

**Thrombosis:** Thrombosis may occur spontaneously in patients with congenital fibrinogen deficiency with or without the use of fibrinogen-replacement therapy. Thromboembolic events have been reported in patients receiving RiaSTAP. The agent’s benefits should be weighed against the risk of thrombosis. Patients should be monitored for signs and symptoms of thrombosis.

**Transmissible infectious agents:** The fibrinogen concentrate continued on page 214
trate is made from human plasma. Products made from human plasma may contain infectious agents (e.g., viruses and, theoretically, the Creutzfeldt–Jakob agent). The risk that such products would transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of current viral infections, and by a process that inactivates or removes some viruses during manufacturing. Despite these measures, plasma products still have the potential to transmit disease. It is also possible that unknown infectious agents may be present in such products. The physician or health care provider should report all infections thought to have been transmitted by RiaSTAP.

**Dosage and Administration:** RiaSTAP is indicated for intravenous use only.

**Therapy for congenital fibrinogen deficiency.** Dosing, the duration of dosing, and the frequency of administration should be adjusted for each individual based on the extent of bleeding, laboratory values, and the patient’s clinical condition.

**When baseline fibrinogen level is known:** The dose should be calculated individually for each patient based on the target plasma fibrinogen level, the type of bleeding, the actual measured plasma fibrinogen level, and body weight according to the following formula:

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\text{dose (mg/kg body weight)} = \frac{\text{target level (mg/dL)} - \text{measured level (mg/dL)}}{1.7 \text{ (mg/dL per mg/kg body weight)}}
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**When the baseline fibrinogen level is unknown:** The recommended dose is 70 mg/kg of body weight administered intravenously. Monitoring the patient’s fibrinogen level is recommended during treatment. A target fibrinogen level of 100 mg/dL should be maintained until hemostasis is attained.

**Commentary:** Fibrinogen, a protein made in the liver, is needed for proper blood clotting. Patients born with fibrinogen deficiency cannot make fibrinogen. This deficiency can be life-threatening if it is not controlled. Congenital fibrinogen deficiency is rare (affecting one person per million). Approximately 300 patients in the U.S. have factor I deficiency. Individuals who inherit an abnormal gene from both parents are vulnerable to fibrinogen deficiency. Symptoms include easy bruising and bleeding from the nose, mouth, and soft tissue. Women with the disorder can experience miscarriage.

RiaSTAP is an orphan drug, indicated for patients with afibrinogenemia and hypofibrinogenemia with bleeding symptoms that may be mild, moderate, or severe. The medication is not indicated for patients with dysfibrinogenemia because they rarely experience bleeding; however, these patients can be susceptible to thrombosis or blood clots. RiaSTAP is used to replace absent or deficient coagulation factor in patients with congenital fibrinogen deficiency during acute bleeding episodes.

**Sources:** www.riastap.com; www.hemophilia.org