Intravenous Human Factor XIII Concentrate (Corifact)

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

**Indication:** Factor XIII concentrate is indicated for the routine prophylactic treatment of Factor XIII deficiency, also called congenital hemophilia A. The drug’s effectiveness is based on maintaining a trough level of 5% to 20%. No controlled trials have shown a direct benefit of Corifact in treating bleeding episodes.

**Biological Class:** The heat-treated, lyophilized concentrate is made from pooled human plasma of healthy donors. Each vial contains 1,000 to 1,600 units of Factor XIII, 120 to 200 mg of human albumin, 120 to 320 mg of total protein, 80 to 120 mg of glucose, and 140 to 220 mg of sodium chloride. Sodium hydroxide is sometimes used to adjust the pH.

**Uniqueness of Biologic Product:** An endogenous plasma glycoprotein, Factor XIII consists of two A-subunits and two B-subunits. Factor XIII, also known as fibrin-stabilizing factor, circulates in blood and is present in platelets, monocytes, and macrophages. It appears in two forms: as a heterotetrameric (A2B2) plasma protein with a molecular weight of about 320 kD and as a homodimeric (A2) cellular form.

Factor XIIIa (activated Factor XIII) promotes the cross-linking of fibrin during coagulation, and it is essential for the physiological protection of the clot against fibrinolysis. It is a transglutaminase enzyme that catalyzes the cross-linking of the fibrin alpha and gamma chains to stabilize fibrin, rendering the fibrin clot more elastic and resistant to fibrinolysis.

Factor XIIIa also cross-links alpha2-plasmin inhibitor to the alpha chain of fibrin, thereby providing protection of the fibrin clot from degradation by plasmin. Cross-linked fibrin, the end result of the coagulation cascade, provides tensile strength to a primary hemostatic platelet plug.

**Warnings and Precautions:**

**Hypersensitivity.** Allergy, rash, pruritus, and erythema have been observed in patients receiving Factor XIII concentrate. If signs or symptoms of anaphylaxis or hypersensitivity reactions occur (such as urticaria, rash, and tightness of the chest, wheezing, and hypotension), Factor XIII therapy should be discontinued immediately and appropriate treatment should be instituted.

**Immunogenicity.** Patients receiving Factor XIII should be monitored for the development of inhibitory antibodies. The presence of inhibitory antibodies may be manifested as an inadequate response to treatment. If expected plasma Factor XIII activity levels are not attained or if breakthrough bleeding occurs during prophylaxis with Factor XIII, an assay to measure inhibitory antibody levels should be performed. Inhibitory antibodies against Factor XIII have been reported in patients with congenital Factor XIII deficiency.

**Thromboembolic risk.** Thromboembolic complications have been reported with the use of Factor XIII. Benefits and risks should be carefully assessed in pregnant women because of their hypercoagulable state and the potential for an increased risk of thromboembolic events.

**Transmission of infectious agents.** Because the Factor XIII product is made from human plasma, it may carry a risk of transmitting viruses, the Creutzfeldt–Jakob disease agent, and other unknown infectious agents. The risk of transmission by these products is reduced because plasma donors are screened for the presence of prior and current viral infections. Although some viruses are inactivated and removed from the product during manufacture, the potential to transmit disease still exists.

Patients who receive Factor XIII concentrate on a regular basis should be vaccinated against hepatitis A and B virus. Any infection thought to have been transmitted by Factor XIII should be reported to CSL Behring or the FDA.

**Monitoring laboratory tests.** Monitoring of trough Factor XIII activity concentrations is recommended during treatment. If breakthrough bleeding occurs or if expected peak plasma Factor XIII activity concentrations are not attained, tests should be performed to determine the presence of Factor XIII inhibitory antibodies.

**Dosage and Administration:** Factor XIII is available as a lyophilized concentrate in a single-use vial containing 1,000 to 1,600 units. A 20-mL vial of Sterile Water for Injection, USP, is provided for reconstitution. The dosing regimen should be tailored to each individual’s weight, laboratory values, and clinical condition.

The initial dose is 40 IU/kg of body weight. The injection rate should not exceed 4 mL/minute. The subsequent dosage should be guided by the most recent trough Factor XIII activity level. Factor XIII should be given every 28 days to maintain a trough activity level of 5% to 20%.

**Commentary:** Factor XIII deficiency is a rare genetic disorder that can cause life-threatening bleeding. One in every 3 million to 5 million people in the U.S. are affected. The condition may cause soft-tissue bruising, spontaneous or fatal intracranial hemorrhage, and umbilical cord bleeding in newborns. A high incidence (2%) of intracranial hemorrhage is a hallmark of the deficiency and a significant cause of morbidity in these patients. In 80% of cases, the first clinical sign is delayed bleeding from the umbilical stump or bleeding following circumcision in newborns.

Corifact was approved as an orphan drug based on a study involving 14 people, including children.

**Sources:** www.corifact.com; MedicineNet, February 17, 2011
Hydroxyprogesterone Caproate Injection (Makena)

**Manufacturer:** Baxter, Bloomington, Ind.

**Indication:** Makena is designed to reduce the risk of preterm birth in women with a singleton pregnancy and a history of a singleton spontaneous preterm birth (defined as less than 37 weeks of gestation). It is not indicated for women with multiple gestations or other risk factors for preterm birth.

**Drug Class:** The chemical name is pregn-4-ene-3,20-dione, 17(1-oxohexyl)oxy. The molecular weight is 428.60. Inactive ingredients include castor oil, benzyl benzoate, and benzyl alcohol as a preservative.

**Uniqueness of Drug:** Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which it reduces the risk of recurrent preterm births is unknown.

**Warnings and Precautions:**

- **Thromboembolic disorders.** The medication should be discontinued if arterial or deep venous thrombosis or a thromboembolism occurs.

- **Allergic reactions.** Urticaria, pruritus, and angioedema have been reported with the use of hydroxyprogesterone and with other products containing castor oil. The practitioner should consider discontinuing therapy if any of these reactions occur.

- **Decreased glucose tolerance.** A reduction in glucose tolerance has been observed in some patients receiving a progestin. The mechanism is unclear. Prediabetic and diabetic women should be monitored while they are receiving hydroxyprogesterone.

- **Fluid retention.** Because progestational drugs may cause fluid retention, women with pre-eclampsia, epilepsy, migraine, asthma, and cardiac or renal dysfunction should be carefully monitored.

- **Depression.** Women with a history of clinical depression should be monitored. Therapy should be discontinued if clinical depression recurs.

- **Jaundice.** Patients who develop jaundice while receiving hydroxyprogesterone caproate should be monitored. The risks and benefits of using this drug should be weighed to determine whether therapy should be continued.

- **Hypertension.** If hypertension develops during hydroxyprogesterone treatment, careful observation is indicated. The risks and benefits of use should be considered to determine whether continued therapy is warranted.

- **Adverse Events:** In a clinical study, complications associated with pregnancy (e.g., miscarriage, stillbirths, hospital admissions for preterm labor, pre-eclampsia, gestational hypertension, gestational diabetes, and low amniotic fluid levels) occurred more often in women receiving the drug than in women who did not receive it.

- **Contraindications:** Hydroxyprogesterone should not be used by women with uncontrolled hypertension; a history of thrombosis or thromboembolic disorders; known or suspected breast cancer or other hormone-sensitive cancer; undiagnosed abnormal vaginal bleeding unrelated to pregnancy; cholestatic jaundice of pregnancy; liver tumors, or active liver disease.

**Dosage and Administration:** The product is injected intramuscularly in the hip area at a dose of 250 mg (1 mL) once weekly. Treatment is initiated between 16 weeks and 20 weeks, six days, of gestation and is continued once weekly until week 37 (through 36 weeks, six days) of gestation or delivery, whichever occurs first. A 5-mL multidose vial (250 mg/mL) contains 1,250 mg of hydroxyprogesterone.

**Commentary:** Hydroxyprogesterone caproate was first approved in 1956 for pregnant women as Delalutin, which Bristol-Myers Squibb withdrew from the market in 2000 for reasons unrelated to safety or efficacy, according to a notice by the FDA published in the Federal Register.

Makena, previously known as Gestiva, was developed by Hologic and was approved under the FDA's accelerated protocol. Hologic recently sold the drug to KV Pharmaceuticals. KV plans to retain Baxter Pharmaceuticals to manufacture the drug; KV’s subsidiary, Ther-Rx, will market it. Makena is available only through a network of specialty pharmacies and distributors.

The drug’s approval represents an opportunity to reduce the number of preterm births, which pose a significant cost of $26 billion to the nation. According to the March of Dimes Foundation, one in eight babies in the U.S. are born before 37 weeks of gestation. The rate of preterm births has increased more than 35% in the last 25 years, and late-preterm births (at 34 to 36 weeks of gestation) account for nearly 75% of all preterm births in the U.S.

To be eligible to take Makena, patients must have previously delivered a premature infant and must be expecting only one infant. Women carrying more than one fetus and women with pre-existing conditions associated with premature births should not take Makena.

This synthetic form of progesterone has been available from compounding pharmacies for years, at a cost of about $10 to $20 per injection. With a single company having won market exclusivity for seven years, Makena may cost as much as $1,500 per dose (possibly $30,000 for one pregnancy). Ther-Rx has said it would offer an assistance program (Makena Cares Connection) for uninsured and low-income women. Despite the cost, FDA oversight of manufacturing should enhance the product’s quality and safety.

KV Pharmaceuticals has received some criticism over the drug’s proposed price of $1,500. The company could face challenges in getting the government and insurance companies to pay. Several members of Congress, the March of Dimes Foundation, the New England Journal of Medicine, the American College of Obstetrics and Gynecology, and the American Academy of Pediatrics have criticized the company for exacting too high a price for a drug it did not invent but will sell under an exclusive marketing agreement. Time will tell whether the company will succumb to pressure and lower the price.

**Sources:** FDA, February 4, 2011; www.makena.com; The Wall Street Journal, Associated Press, March 10, 2011

Azilsartan Medoxomil Tablets (Edarbi)

**Manufacturer:** Takeda Pharmaceuticals, Deerfield, Ill.

**Indication:** Edarbi is an angiotensin II receptor blocker (ARB) used in the treatment of hypertension, either alone or in combination with other antihypertensive agents.

**Drug Class:** Azilsartan medoxomil, a prodrug, is hydrolyzed to azilsartan in the gastrointestinal (GI) tract during absorption. It is a selective AT1 subtype angiotensin II receptor antagonist. The drug is the potassium salt of azilsartan.
medoxomil. Its chemical name is (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl-2-ethoxy-1-(4′,5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl)methyl-1H-benimidazole-7-carboxylate monopotassium salt.

**Uniqueness of Drug:** Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzymes (ACE, kinase II). Angiotensin II is the principal pressor agent of the renin–angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Azilsartan inhibits the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues (e.g., vascular smooth muscle and the adrenal gland). Its action, therefore, is independent of the pathway for angiotensin II synthesis. An AT2 receptor is also found in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis.

Azilsartan has more than a 10,000-fold greater affinity for the AT1 receptor than for the AT2 receptor. Blockade of the renin–angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used to treat blood pressure (BP). These medications also inhibit the degradation of bradykinin, a reaction catalyzed by ACE. Because azilsartan does not inhibit kinase II, it should not affect bradykinin levels. It is not known whether this difference is relevant. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of azilsartan on BP.

**Warnings and Precautions:**

**Fetal and neonatal effects.** Drugs that act directly on the renin–angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women during the second and third trimesters. If pregnancy is confirmed, azilsartan medoxomil should be discontinued as soon as possible. In fewer than one in every 1,000 pregnancies, no alternative drugs that act on the renin–angiotensin system may be available. If azilsartan is used, the mother should be apprised of the potential hazards to the fetus, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If a deficiency of amniotic fluid is observed, the drug should be discontinued unless it is considered life-saving for the mother. Patients and physicians should be aware, however, that oligohydramnios might not appear until after the fetus has sustained irreversible injury. An infant with a history of in utero exposure to an ARB should be closely observed for hypotension, oliguria, and hyperkalemia.

**Hypotension in patients with volume or salt depletion.** In patients with an activated renin–angiotensin system, such as those using high doses of diuretics, symptomatic hypotension may occur after azilsartan medoxomil is initiated. Volume or salt depletion should be corrected before therapy is begun, or the initial dose should be 40 mg. If hypotension does occur, the patient should be placed in the supine position and, if necessary, should be given an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty after BP has stabilized.

**Impaired renal function.** As a result of inhibiting the renin–angiotensin system, azilsartan medoxomil may cause changes in renal function. In patients whose renal function may depend on the activity of the renin–angiotensin system (such as those with severe congestive heart failure, renal artery stenosis, or volume depletion), ACE inhibitors and ARBs have been associated with oliguria or progressive azotemia but rarely with acute renal failure and death. Similar results may be anticipated in patients who take azilsartan medoxomil.

Studies of ACE inhibitors in patients with renal artery stenosis have shown increases in serum creatinine or blood urea nitrogen. The long-term use of azilsartan in patients with unilateral or bilateral renal artery stenosis has not been studied, but similar results may be expected.

**Dosage and Administration:** The recommended adult dose of azilsartan medoxomil is 80 mg once daily. A starting dose of 40 mg might be considered for patients taking high doses of diuretics. Azilsartan medoxomil may be taken with other antihypertensive agents.

**Drug Interactions:** No clinically significant drug interactions have been observed in studies of azilsartan medoxomil or azilsartan when taken with amlodipine (Norvasc, Pfizer), antacids, chlorothalidone (Thalitone, Monarch/King), digoxin (Lanoxin, GlaxoSmithKline), fluconazole (Diflucan, Pfizer), glyburide (DiaBeta, Sanofi-Aventis), ketocconazole (Nizoral, PriCara), metformin (Glucophage, Bristol-Myers Squibb), piroglitazone (Actos, Takeda), or warfarin (Coumadin, Bristol-Myers Squibb).

**Commentary:** Azilsartan medoxomil is an ARB that lowers BP by blocking the action of angiotensin II, a vasopressor hormone. In clinical trials, azilsartan medoxomil was more effective than valsartan (Diovan, Novartis) and olmesartan (Benicar, Daiichi Sankyo) in lowering BP over 24 hours. Approximately 75 million Americans (nearly one in three adults) and nearly one billion people worldwide have high BP. This figure is expected to increase to 1.5 billion by the year 2025. Risk increases with age. More than 50% of people older than 60 years of age are affected.

The American Heart Association estimates that direct and indirect expenses associated with hypertension cost the nation more than $73 billion in 2009.

**Sources:** www.edarbi.com; http://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?id=39324&type=display