Coagulation Factor IX (Recombinant), Albumin Fusion Protein (Idelvion)

Manufacturer: CSL Behring LLC, King of Prussia, Pennsylvania

Date of Approval: March 4, 2016

Indication: Idelvion is a long-acting albumin fusion protein linking recombinant coagulation factor IX with recombinant albumin. Idelvion was approved for use in children and adults with hemophilia B for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; for on-demand control and prevention of bleeding episodes; and for the perioperative management of bleeding. Idelvion is not indicated for immune tolerance induction in patients with hemophilia B.

Drug Class: Blood coagulation factors

Uniqueness of Drug: Hemophilia B, a rare inherited disorder, prevents blood from clotting normally, which leaves patients at risk for potentially serious bleeding. Idelvion is used to replace factor IX, a naturally occurring clotting factor that is missing or defective in people with the condition. Idelvion is the first coagulation factor-albumin fusion protein product to be approved, and the second factor IX fusion protein product approved in the U.S. that is modified to last longer in the blood.

Warnings and Precautions:

Hypersensitivity reactions. Hypersensitivity reactions may occur and can progress to anaphylaxis. These reactions include chest tightness, generalized urticaria, hypotension, dyspnea, angioedema, and wheezing. If any symptoms occur, discontinue administration immediately and initiate appropriate treatment. Idelvion contains trace amounts of Chinese hamster ovary proteins. Patients treated with this product may develop hypersensitivity to these nonhuman mammalian proteins.

Neutralizing antibodies. Development of neutralizing antibodies (inhibitors) to Idelvion may occur. If expected factor IX plasma recovery in patient plasma is not attained or if bleeding is not controlled with an appropriate dose, perform an assay that measures factor IX inhibitor concentration.

Thromboembolic complications. Thromboembolism, such as pulmonary embolism, venous thrombosis, or arterial thrombosis, can occur when using factor IX-containing products. Because of this potential risk, monitor for early signs of thromboembolism and consumptive coagulopathy in patients with liver disease, fibrinolysis, perioperative status, or risk factors for thromboembolic events or disseminated intravascular coagulation.

Nephrotic syndrome. Nephrotic syndrome has been reported following immune tolerance induction with factor IX-containing products in hemophilia B patients with factor IX inhibitors and a history of allergic reactions to factor IX.

Monitoring laboratory tests. Monitor factor IX plasma levels with a one-stage clotting assay to confirm that adequate factor IX levels have been achieved and maintained. Factor IX activity assay results may vary with the type of activated partial thromboplastin time reagent used in the assay system.

Dosage and Administration: Idelvion is administered intravenously, and the infusion rate should not exceed 10 mL/min. The dosage and duration of treatment depends on the severity of the factor IX deficiency, the location and extent of bleeding, and the patient’s clinical condition, age, and recovery of factor IX. The initial dose is determined using the following formula:

Required Dose (IU) = Body Weight (kg) x Desired Factor IX Rise (% of normal or IU/dL) x (Reciprocal of Recovery [IU/kg per IU/dL])

For routine prophylaxis, the recommended dose for patients 12 years of age or older is 25–40 IU/kg body weight every seven days. Patients who are well controlled on this regimen may be switched to a 14-day interval at 50–75 IU/kg body weight. For patients younger than 12 years of age, the dose is 40–55 IU/kg body weight every seven days.

Commentary: In clinical trials, Idelvion maintained factor IX activity levels above 5% over 14 days, resulting in a median annualized spontaneous bleeding rate of zero. The data for on-demand therapy showed that 94% of bleeds were controlled with one infusion, while 99% were controlled with one or two infusions. The most common adverse reaction in clinical trials was headache.

Sources: CSL Behring LLC, Idelvion prescribing information

Captisol-Enabled Melphalan HCl (Evomela)

Manufacturer: Spectrum Pharmaceuticals, Inc., Irvine, California

Date of Approval: March 10, 2016

Indication: Evomela, an alkylating drug, is indicated for use as a high-dose conditioning treatment prior to hematopoietic stem cell transplant (HSCT) in patients with multiple myeloma and palliative treatment of patients with multiple myeloma who cannot take oral therapy.

Drug Class: Nitrogen mustard analogues

Uniqueness of Drug: Evomela is the first drug approved for the high-dose conditioning indication in multiple myeloma and has been granted orphan drug designation by the FDA. It is a new formulation of melphalan that is free of propylene glycol. The use of Captisol, a specially modified cyclodextrin, improves the solubility and stability of melphalan, and thus eliminates the need for propylene glycol, which can cause complications, such as metabolic/renal dysfunction and arrhythmias.

Warnings and Precautions: There is a boxed warning for severe bone marrow suppression, hypersensitivity, and leukemogenicity.

Bone marrow suppression. Myeloablation occurs in all patients receiving Evomela as part of a conditioning regimen.

Sources: Spectrum Pharmaceuticals, Inc., Evomela prescribing information

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Pharmaceutical Approval Update

If a stem cell product is not available for rescue, do not begin the conditioning regimen. Monitor complete blood counts and provide supportive care for infections, anemia, and thrombocytopenia until there is adequate hematopoietic recovery. For patients receiving Evomela as palliative treatment, if the bone marrow has been compromised by prior irradiation or prior chemotherapy, or is recovering from chemotherapy, the risk of severe myelosuppression with Evomela is increased. Perform periodic complete blood counts during the course of treatment with Evomela. Provide supportive care for infections, bleeding, and symptomatic anemia.

**Gastrointestinal toxicity.** Nausea, vomiting, mucositis, and diarrhea may occur in more than 50% of patients receiving Evomela as part of a conditioning regimen. Use prophylactic antiemetic medication and provide supportive care for nausea, vomiting, diarrhea, and mucositis. The frequency of grade 3/4 mucositis in clinical studies was 13%. Provide nutritional support and analgesics for patients with severe mucositis. For patients receiving Evomela as palliative treatment, nausea, vomiting, diarrhea, and oral ulceration may occur. Use prophylactic antiemetics and provide supportive care for nausea, vomiting, diarrhea, and mucositis.

**Hepatotoxicity.** Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported after treatment with melphalan. Hepatic veno-occlusive disease has also been reported. Monitor liver chemistries.

**Hypersensitivity.** Approximately 2% of patients who received an intravenous (IV) formulation of melphalan have had acute hypersensitivity reactions, including anaphylaxis. Symptoms may include urticaria, pruritus, edema, and skin rashes and, in some patients, tachycardia, bronchospasm, dyspnea, and hypotension. If serious hypersensitivity reactions occur, discontinue treatment with Evomela.

**Secondary malignancies.** Melphalan has been shown to cause chromatid or chromosome damage in humans. Multiple myeloma patients treated with melphalan-containing chemotherapy regimens have developed secondary malignancies, such as myeloproliferative syndrome or acute leukemia. The potential benefit of Evomela therapy must be considered against the possible risk of the induction of a secondary malignancy.

**Embryo-fetal toxicity.** Based on its mechanism of action, Evomela can cause fetal harm when administered to a pregnant woman. Melphalan is genotoxic, targets actively dividing cells, and was embryo-lethal and teratogenic in rats. Advise women of reproductive potential to avoid pregnancy during and after treatment with Evomela. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, advise the patient of potential risk to the fetus.

**Infertility.** Suppression of ovarian function in premenopausal women undergoing melphalan-based chemotherapy regimens has been reported, resulting in persistent amenorrhea in approximately 9% of patients. Reversible or irreversible testicular suppression has also been reported.

**Dosage and Administration:** The recommended dose of Evomela for conditioning treatment is 100 mg/m² per day administered over 30 minutes by IV infusion for two consecutive days (day –3 and day –2) prior to autologous stem cell transplantation (day 0). For patients who weigh more than 130% of their ideal body weight, body surface area should be calculated based on adjusted ideal body weight. The recommended dose of Evomela for palliative treatment is 16 mg/m² administered as a single IV infusion over 15–20 minutes at two-week intervals for four doses, then, after adequate recovery from toxicity, at four-week intervals. Administer prophylactic antiemetics with both conditioning treatment and palliative treatment.

**Commentary:** The safety of Evomela was evaluated in 61 patients with multiple myeloma in a single-arm clinical trial in which patients were given Evomela at a dosage of 100 mg/m² per day administered over approximately 30 minutes (range, 24–48 minutes) by IV infusion for two consecutive days (day –3 and day –2) prior to autologous stem cell transplant (day 0). Efficacy was assessed by clinical response at day +100. There was an overall response rate (ORR) of 95% and a complete response (CR) rate of 31% (16% stringent CRs), as determined by investigator assessment. The ORR was 100% and the CR rate was 21% on independent pathology review. The lower rate of confirmed CRs in the independent review was related to missing data. All study participants achieved myeloablation a median of five days after HSCT, all had successful neutrophil engraftment a median of 12 days after HSCT, and all had platelet engraftment a median of 13 days after HSCT. The most common adverse reactions observed in at least 50% of patients with multiple myeloma treated with Evomela were decreased neutrophil count, decreased white blood cell count, decreased lymphocyte count, decreased platelet count, diarrhea, nausea, fatigue, hypokalemia, anemia, and vomiting.

**Sources:** Spectrum Pharmaceuticals, Inc., Evomela prescribing information

**Antihemophilic Factor (Recombinant) (Kovaltry)**

**Manufacturer:** Bayer HealthCare, LLC, Whippany, New Jersey

**Date of Approval:** March 17, 2016

**Indication:** Kovaltry is a recombinant, human DNA sequence-derived, full-length factor VIII concentrate indicated for use in adults and children with hemophilia A (congenital factor VIII deficiency) for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes. Kovaltry is not indicated for the treatment of von Willebrand disease.

**Drug Class:** Blood coagulation factors

**Uniqueness of Drug:** Kovaltry is an unmodified, full-length factor VIII compound that temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis. Clinical trials supported the approval of Kovaltry for routine prophylaxis to reduce the frequency of bleeding episodes.

**Warnings and Precautions:**

**Hypersensitivity reaction.** Kovaltry may cause hypersensitivity reactions, including anaphylaxis. Early signs of hypersensitivity reactions, which can progress to anaphylaxis, may include chest or throat tightness, dizziness, mild hypotension, and nausea. Discontinue Kovaltry if symptoms occur and seek immediate emergency treatment. Kovaltry may contain trace amounts of mouse and hamster proteins, and patients treated with this product may develop hypersensitivity to these

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nonhuman mammalian proteins.

**Neutralizing antibodies.** Neutralizing antibody (inhibitor) formation can occur following administration of Kovaltry. Previously untreated patients are at greatest risk for inhibitor development with all factor VIII products. Carefully monitor patients for the development of factor VIII inhibitors, using appropriate clinical observations and laboratory tests. If expected plasma factor VIII activity levels are not attained or if bleeding is not controlled as expected with administered dose, suspect the presence of an inhibitor (neutralizing antibody).

**Cardiovascular risk factors.** Hemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as nonhemophilic patients when clotting has been normalized by treatment with factor VIII.

**Catheter-related infections.** Catheter-related infections may be observed when Kovaltry is administered via central venous access devices. These infections have not been associated with the product itself.

**Monitoring laboratory tests.** Monitor plasma factor VIII activity levels using a validated test to confirm that adequate factor VIII levels have been achieved and maintained. Monitor for development of factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected factor VIII plasma levels are not attained or if bleeding is not controlled with the expected dose of Kovaltry. Use Bethesda units to report inhibitor titers.

**Dosage and Administration:** Kovaltry is for intravenous use after reconstitution and it is available with a vial adapter or bio-set. For control of bleeding episodes and perioperative management, the dose is determined using the following formulas:

1. Required dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (% of normal or IU/dL) x Reciprocal of Expected/Observed Recovery (e.g., 0.5 for a recovery of 2 IU/dL per IU/kg)
2. Estimated Increment of Factor VIII (IU/dL or % of normal) = \[\text{Total Dose (IU)/Body Weight (kg)}\] x 2 (IU/dL per IU/kg)

For routine prophylaxis in adults and adolescents, the dose is 20–40 IU/kg two or three times per week. The use with a bio-set has an additional approved dose for children 12 years old or younger and it is 25–50 IU/kg two times per week, three times per week, or every other day.

**Commentary:** The Long-Term Efficacy Open-Label Program in Severe Hemophilia A Disease (LEOPOLD) clinical development program consisted of three multinational clinical trials that evaluated the pharmacokinetics, efficacy, and safety of Kovaltry in patients with severe hemophilia A (less than 1% factor VIII:C). The combined trials evaluated Kovaltry in more than 200 children and adults with severe hemophilia A from 60 sites in 25 countries worldwide.

Clinical trial results demonstrate that Kovaltry controls bleeds and reduces frequency of bleeding episodes with routine prophylaxis in children and adults with hemophilia A when used two or three times per week. The most frequently reported adverse reactions in the clinical trials (3% or more) were headache, pyrexia, and pruritus.

**Sources:** Bayer HealthCare, LLC, Kovaltry prescribing information