Fostamatinib Disodium Hexahydrate (Tavalisse)

**Manufacturer:** Rigel Pharmaceuticals, Inc., South San Francisco, California

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

**Indication:** Fostamatinib is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

**Drug Class:** Immunomodulator

**Uniqueness of Drug:** Fostamatinib is an oral spleen tyrosine kinase inhibitor that targets the underlying autoimmunity of the disease by impeding platelet destruction, providing an important new treatment option for adult patients with chronic ITP.

**Warnings and Precautions:**

**Hypertension.** Monitor patient blood pressure every two weeks until stable, then monthly thereafter. Manage hypertension using standard antihypertensive treatment and, if needed, interrupt, reduce, or discontinue fostamatinib.

**Hepatotoxicity.** Monitor patient liver function tests (LFTs) monthly. If LFT levels are elevated, interrupt, reduce, or discontinue fostamatinib.

**Diarrhea.** Diarrhea occurred in 31% of patients treated with fostamatinib. Manage diarrhea with supportive measures. If diarrhea becomes severe, interrupt, reduce, or discontinue fostamatinib.

**Neutropenia.** Neutropenia occurred in 6% of patients treated with fostamatinib. Monitor patient absolute neutrophil count monthly, and monitor for infection. If neutrophil count decreases below 1.0 x 10^9/L, interrupt, reduce, or discontinue fostamatinib.

**Embryo-fetal toxicity.** Fostamatinib can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

**Dosage and Administration:** Fostamatinib is initiated at a dose of 100 mg taken orally twice daily. After four weeks, it may be increased to 150 mg twice daily, if needed, to achieve a platelet count of at least 50 x 10^9/L as necessary to reduce the risk of bleeding. Discontinue fostamatinib after 12 weeks of treatment if the patient’s platelet count does not increase to a level sufficient to avoid clinically important bleeding.

Fostamatinib may be taken with or without food. In the case of a missed dose, instruct patients to take their next dose at its regularly scheduled time.

**Commentary:** The Food and Drug Administration’s approval of fostamatinib was supported by data from a phase 3 clinical program that included three studies that evaluated fostamatinib in 163 patients with ITP. The new drug application was also supported by a safety database of more than 4,600 patients across other indications for which fostamatinib has been evaluated. The most common adverse reactions occurring in 5% or more of those treated with the drug are diarrhea, hypertension, nausea, respiratory infection, dizziness, increased alanine aminotransferase/aspartate aminotransferase, rash, abdominal pain, fatigue, chest pain, and neutropenia.

**Sources:** Rigel Pharmaceuticals, Inc., Tavalisse prescribing information

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Coagulation Factor Xa (Recombinant), Inactivated-zhzo (Andexxa)

**Manufacturer:** Portola Pharmaceuticals, Inc., South San Francisco, California

**Date of Approval:** May 4, 2018

**Indication:** Andexxa is a recombinant modified human factor Xa (FXa) protein indicated for patients treated with rivaroxaban (Xarelto, Janssen) or apixaban (Eliquis, Bristol-Myers Squibb) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. This indication is received accelerated approval from the Food and Drug Administration (FDA) based on the change from baseline in anti-FXa activity in healthy volunteers.

**Drug Class:** Factor Xa inhibitor antidote

**Uniqueness of Drug:** Andexxa is the first and only antidote indicated to reverse the anticoagulation effects of factor Xa inhibitors, such as rivaroxaban and apixaban, when patients are experiencing uncontrolled or life-threatening bleeding.

**Warnings and Precautions:**

**Boxed warning: thromboembolic risks, ischemic risks, cardiac arrest, and sudden deaths.** Treatment with Andexxa has been associated with serious and life-threatening adverse events, including: arterial and venous thromboembolic events; ischemic events, including myocardial infarction and ischemic stroke; cardiac arrest; and sudden deaths. Monitor patients for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.

**Re-elevation or incomplete reversal of anti-FXa activity.** Although anti-FXa activity following Andexxa administration was consistent in the healthy volunteer studies and the ANNEXA-4 study in bleeding patients, re-elevation or incomplete reversal of anticoagulant activity can occur.

**Dosage and Administration:** Andexxa is for intravenous (IV) use only. It is administered as an IV bolus, with a target rate of 30 mg/min, followed by continuous infusion for up to 120 minutes. The recommended dose of Andexxa is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient’s last dose of FXa inhibitor. Consult the full prescribing information to calculate patient-appropriate dosing.

**Commentary:** The FDA approval of Andexxa was based on two phase 3 studies, which evaluated the safety and efficacy of Andexxa in reversing the anticoagulant activity of rivaroxaban and apixaban in healthy participants. The data showed Andexxa quickly and significantly reversed anti-FXa activity. The median decrease in anti-FXa activity from baseline was 97% for rivaroxaban and 92% for apixaban. In addition, the FDA also reviewed interim data from the ANNEXA-4 trial, a single-arm, open-label study in patients with major bleeding. Among the evaluable...
patients (N = 185), Andexxa quickly and significantly reversed anti-FXa activity when given as a bolus; the effect was sustained when followed by a 120-minute infusion. The median decrease from baseline was 90% for rivaroxaban and 93% for apixaban. The most common adverse reactions occurring in 5% or more of patients receiving Andexxa were urinary tract infections and pneumonia. The most common adverse reactions occurring in 3% or more of healthy volunteers treated with Andexxa were infusion-related reactions.

**Sources:** Fortola Pharmaceuticals, Inc., Andexxa prescribing information

**Epoetin Alfa-epbx (Retacrit)**

**Manufacturer:** Hospira, Inc., Lake Forest, Illinois

**Date of Approval:** May 15, 2018

**Indication:** The Food and Drug Administration (FDA) approved Retacrit as a biosimilar to epoetin alfa for the treatment of anemia caused by chronic kidney disease (CKD), chemotherapy, or use of zidovudine in patients with human immunodeficiency virus (HIV) infection. Retacrit is also approved for use before and after surgery to reduce the chance that red blood cell transfusions will be needed because of blood loss during surgery.

**Drug Class:** Biosimilar, erythropoiesis-stimulating agent (ESA)

**Uniqueness of Drug:** Retacrit is the first and only biosimilar ESA approved in the U.S. It must be dispensed with a patient Medication Guide that provides information about the drug’s uses and risks.

**Warnings and Precautions:**

**Boxed warning.** ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence. See the full prescribing information for details of this warning for patients with CKD or cancer, and for patients undergoing surgery.

**Hypertension.** Retacrit is contraindicated in patients with uncontrolled hypertension. Appropriately control patients’ hypertension prior to initiation of and during treatment with Retacrit. Reduce or withhold the agent if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions.

**Seizures.** Epoetin alfa products increase the risk of seizures in patients with CKD. During the first several months following initiation of Retacrit, monitor patients closely for premonitory neurological symptoms. Advise patients to contact their health care practitioner for new-onset seizures, premonitory symptoms, or change in seizure frequency.

**Pure red cell aplasia (PRCA).** Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin, have been reported in patients treated with epoetin alfa. This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. If severe anemia and low reticulocyte count develop during treatment with Retacrit, withhold the agent and evaluate patients for neutralizing antibodies to erythropoietin.

**Serious allergic reactions.** Immediately and permanently discontinue Retacrit and administer appropriate therapy if a serious allergic or anaphylactic reaction occurs.

**Severe cutaneous reactions.** Discontinue Retacrit therapy immediately if a severe cutaneous reaction, such as Stevens–Johnson syndrome/toxic epidermal necrolysis, is suspected.

**Risk in patients with phenylketonuria.** Retacrit contains phenylalanine, which can be harmful to patients with phenylketonuria (PKU). Before prescribing Retacrit to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including Retacrit.

**Dosage and Administration:** Evaluate iron status before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia before initiating treatment.

In patients with CKD, the recommended initial dose is 50–100 units/kg three times weekly (adult) and 50 units/kg three times weekly (pediatric). Individualize maintenance doses. Intravenous (IV) administration is recommended for patients on hemodialysis.

For patients with HIV infection taking zidovudine, the recommended dose is 100 units/kg three times weekly.

Adult patients with cancer on chemotherapy may be administered 40,000 units weekly or 150 units/kg three times weekly (adults). For pediatric patients (older than 5 years of age) with cancer on chemotherapy the recommended dose is 600 units/kg IV once weekly.

Patients undergoing surgery may be administered 300 units/kg per day daily for 15 days or 600 units/kg weekly.

**Commentary:** The FDA's approval of Retacrit was based on a review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data.

Retacrit has been approved as a biosimilar to epoetin alfa, not as an interchangeable product. The most common adverse reactions occurring in 5% or more of patients were hypertension, arthralgia, muscle spasm, pyrexia, dizziness, medical device malfunction, vascular occlusion, upper respiratory tract infection, nausea, vomiting, myalgia, stomatitis, cough, weight decrease, leukopenia, bone pain, rash, hyperglycemia, insomnia, headache, depression, hypokalemia, chills, deep vein thrombosis, and injection-site irritation.

**Sources:** Hospira, Inc., Retacrit prescribing information

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Pharmaceutical Approval Update

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