

Brand Name^{1,2}: Rixubis

Generic Name^{1,2}: Coagulation factor IX recombinant

Manufacturer⁵: Baxter

Drug Class^{1,2,3}: Antihemophilic agent

Labeled Uses^{1,2}: Hemophilia B – hemorrhage, routine prophylaxis, perioperative care

Mechanism of Action¹: Coagulation factor IX recombinant is used to temporarily replace coagulation factor IX in patients with hemophilia. A complex of factor VII and tissue factor (via the extrinsic coagulation pathway) and factor XIa (via the intrinsic pathway) activate factor IX. This, in combination with factor VIII, activates factor X. Prothrombin is then converted to thrombin through this pathway, which, in turn, converts fibrinogen to a fibrin clot.

Pharmacokinetics¹:

Half-life^{1,2}	18.8-25.4 hr
Tmax⁴	66.2 min
Vd^{1,2}	178.6 mL/kg
Clearance^{1,4}	6 mL/(kg x hr)
Protein binding	N/A
Bioavailability	N/A

Metabolism: N/A

Elimination: N/A

Efficacy:

Citation⁶: Windyga J, Lissitchkov T, Stasyhyn O, Mamonov V, Rusen L, Lamas JL, et al. Pharmacokinetics, efficacy and safety of BAX326 (Rixubis), a novel recombinant factor IX: a prospective, controlled, multicenter phase I/III study in previously treated patients with severe (FIX level < 1%) or moderately severe (FIX level ≤ 2) hemophilia B. Haemophilia 2013:1-10.

Study design: Multicenter, randomized, controlled, cross-over, blinded PK comparison

Description: Rixubis is a recombinant factor IX. The aim of this trial was to investigate the pharmacokinetics, hemostatic efficacy, and safety of Rixubis in previously treated patients aged 12-65 years with severe or moderately severe hemophilia B. The study included a randomized, blinded PK crossover segment comparing Rixubis with a licensed comparator, and an open-labeled treatment segment, in which subjects received Rixubis either as twice-weekly prophylaxis or on-demand. The objective of the PK segment was to characterize the PK profile of Rixubis and determine PK equivalence with a commercial factor IX product. The initial treatment regimen during the open-label treatment segment consisted of twice-weekly prophylaxis with Rixubis. During the course of the study, the design was adapted to include subjects to be treated with Rixubis for acute bleeds only (on-demand). Subjects treated on-demand were enrolled

after completion of enrollment of the prophylaxis treatment arm. Dosing for the on-demand treatment was calculated by body weight (kg) x desired FIX rise (% or IU/dL) x 1.3 IU/kg, according to the severity of the bleed. Bleeds were treated either at home or at the study site. The trial was conducted between July 2010 and May 2012. **Methods:** infusion of Rixubis or comparator rFIX (75 +/- 5 IU/kg) with a 5-7 day washout between treatments. **Outcome results:** Rixubis was safe and well tolerated in all 73 treated subjects. Adverse events considered related to treatment were transient and mild, and no hypersensitivity reactions, inhibitor formation, or thrombotic events were observed. Pharmacokinetic equivalence was confirmed between the two groups as shown by the ratio of geometric mean AUC per dose. Twice weekly prophylaxis was effective in preventing bleeding episodes, with a significantly lower annualized bleed rate compared to on-demand treatment in a historical control group. Of 249 total acute bleeds, 211 were controlled with 1-2 infusions of Rixubis. Hemostatic efficacy at resolution of bleed was rated excellent or good in 96% of all treated bleeding episodes.

Limitations: Bias may be an issue in this study as Baxter funded the study and multiple authors are employees of Baxter. The study population was small and a 90% confidence interval was used, making the results hard to extrapolate to the true population.

Conclusions: The results of this study indicate that Rixubis is safe and efficacious in treating bleeds and routine prophylaxis in patients aged 12 years and older with hemophilia B.

Citation⁷: Roth DA, Kessler CM, Pasi J, Rup B, Courter SG, Tubridy KL. Human recombinant factor IX: safety and efficacy studies in hemophilia B patients previously treated with plasma-derived factor IX concentrates. *Blood* 2001;98(13):3600-3606.

Study design: Observational

Description: The study comprised pharmacokinetic assessment; assessment of thrombogenicity, and safety and efficacy during home treatment and management of surgical procedures. **Methods:** A baseline PK evaluation was performed on first infusion with rFIX. The PK parameters were derived using the observed maximum factor IX activity and the elimination half-life. Fibrinopeptide A and prothrombin fragment were measured to assess thrombogenicity in participants. For safety, the prescribed dosing regimen was based on body weight, vial potency, and the nature of the hemorrhage or surgery following standard guidelines. The PK assessment was repeated every 6 months, with routine clinical and laboratory evaluations at 3-month intervals. The planned study duration for each participant was 2 years. **Outcome results:** 50 subjects completed the 24-month study. Repeat PK assessments every 6 months demonstrated the stability of the parameters during 2 years of exposure to rFIX. No significant reduction in baseline rFIX recovery or elimination half-life occurred in any previously treated patients over time with the exception of one. Subgroup analyses revealed the lowest recoveries in subjects younger than 15 years old as well as those patients who were negative for factor IX antigen, although neither reached statistical significance. 27 surgical procedures were performed in 20 patients, and estimated blood loss was comparable to

individuals without a coagulation disorder. Additionally there was no evidence of transmission of HAV, HBV, HCV, HIV-1, or HIV-2.

Limitations: The study design with a small sample size can limit the true effects of Rixubis. There was no randomization of the study sample and no control was used for comparison.

Conclusions: Based on the outcomes, Rixubis provides a new option for the safe and effective management of bleeding in patients with hemophilia B. However, due to study design limitations, further studies would need to be done to confirm this result.

Contraindications^{1,3}:

- Disseminated intravascular coagulation (DIC)
- Signs of fibrinolysis
- Hypersensitivity to coagulation factor IX recombinant, hamster protein, or any component of the product

Precautions^{1,3}:

- Factor IX inhibitor development; increased risk of severe hypersensitivity reactions including anaphylaxis; monitoring recommended
- Fibrinolysis, peri- and postoperative signs; increased risk of thromboembolic events (pulmonary embolism, venous thrombosis, arterial thrombosis); monitoring recommended
- Hamster protein component; hypersensitivity may develop
- Hepatic disease; increased risk of thromboembolic events; monitoring recommended
- Hypersensitivity reactions, including anaphylaxis, have been reported; increased risk during first exposures in treatment-naive patients, particularly those with high-risk gene mutations; discontinue use if suspected
- Nephrotic syndrome has occurred following attempted immune tolerance induction with factor IX inhibitors
- Patients at high-risk for thrombotic events or disseminated intravascular coagulation; increased risk of thromboembolic events; monitoring recommended
- Thromboembolic events have been reported with the use of factor X containing products; monitoring recommended

Adverse Effects^{1,3}:

Common:

Cardiovascular: flushing (3%), chest tightness (2%)

Central Nervous System: headache (11%), dizziness (8%), fever (3%), drowsiness (2%), chills (2%)

Dermatologic: rash (2-6%), urticarial (3-5%)

Gastrointestinal: taste sense altered (5%), nausea (6%), vomiting (2%)

Immunologic: antibody development (14.3%)

Local: injection reaction (2-8%, including cellulitis, pain, phlebitis)

Ocular: blurred vision (2%)

Renal: renal infarct (2%)

Respiratory: dyspnea (3%), cough (2%), hypoxia (2%)

Miscellaneous: shaking (2%)

Serious [limited to important or life-threatening] (< 1%):

Anaphylaxis, angioedema, bronchospasm, DVT, hypersensitivity reactions, hypotension, inadequate response/recovery, nephrotic syndrome, peripheral thrombophlebitis, superior vena cava syndrome (neonates), thrombosis, wheezing

Drug Interactions^{2, 3}:

Aminocaproic Acid: may enhance the adverse/toxic effect of Factor IX. Specifically, use of this combination may increase the risk of thrombosis. Avoid combination.

Dosing/Administration^{1, 4}:

Adult dosing:

Formula for units required to raise blood level %: Number of factor IX units required = patient weight (kg) x desired factor IX level increase (% or units/dL) x 1.3 (units/kg per units/dL)

Note: If patient has severe hemophilia (baseline factor IX level is or presumed to be <1%), then may just use "desired factor IX level" instead of "desired factor IX level increase"

Hemorrhage

Initial dose = body weight (kg) times desired factor IX increase (% of normal or IU/dL) times reciprocal of observed recovery (IU/kg per IU/dL), IV

Number of recombinant factor IX complex IU required = body weight (kg) times desired factor IX increase (% or IU/dL) times 1.1 dL/kg, IV

Mild hemorrhage: (20-30% of normal factor IX level or 20-30 IU/dL factor IX activity required) IV every 12-24 hours for at least 1 day, until healing is achieved

Moderate hemorrhage: (25-50% of normal factor IX level or 25-50 IU/dL activity required) IV every 12-24 hours for 2-7 days

Major hemorrhage: (50-100% of normal factor IX level or 50-100 IU/dL activity required) IV every 12-24 hours for 7-10 days

Routine prophylaxis: Rixubis – previously treated patients, 40-60 IU/kg IV, twice a week; titrate as necessary for individual age, bleeding pattern, and physical activity. Specific maximum dosage information is not available. Individualize dosage based on the location and severity of the bleed or type of procedure, the clinical status of the patient, the factor IX activity concentration, and the presence of factor IX inhibitors.

Perioperative care

Initial dose = body weight (kg) times desired factor IX increase (% of normal or IU/dL) times reciprocal of observed recovery (IU/kg per IU/dL), IV

Number of recombinant factor IX complex IU required = body weight (kg) times desired factor IX increase (% or IU/dL) times 1.1 dL/kg, IV

Minor surgery: 30-60 IU/dL or 30-60% of normal factor IX level required, IV every 24 hours for 1 or more days until healing is achieved

Major surgery: 80-100 IU/dL or 80-100% of normal factor IX level required, IV every 8-24 hours for 7-10 days until bleeding stops and healing is achieved

**IU = international units*

Pediatric dosing^{2, 5}:

Safety and efficacy have not been established in pediatric patients

Hepatic Impairment²:

No dosage adjustments are needed

Renal Impairment²:

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed

Use in Special Circumstances:

Pregnancy^{1, 2}:

Category C

It is not known whether factor IX products can affect reproductive capacity or cause fetal harm when given to pregnant women. Factor IX products should be administered to pregnant women only if clearly indicated.

Lactation¹:

Infant risk cannot be ruled out: available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

Conclusion: Rixubis is indicated for bleeding control associated hemorrhage, routine prophylaxis, or perioperative care. It has proven efficacy with few serious side effects, and it has no need for dose adjustments in those patients with hepatic or renal insufficiency. Also, unlike plasma-derived factor IX, it has not been shown to transmit HAV, HBV, HCV, HIV-1, or HIV-2. However, Rixubis only contains factor IX and thus is not indicated for replacement therapy of any other clotting factor besides factor IX or for reversal of anticoagulation due to either vitamin K antagonists or other anticoagulants, for hemophilia A patients with factor VIII inhibitors, or for patients in a hemorrhagic state caused by reduced production

of liver-dependent coagulation factor. Overall, it is a safe and effective treatment for patients with hemophilia B that meet the listed indications.

Recommended References:

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4. Rixubis [package insert]. Westlake Village, Ca: Baxter Healthcare Corporation; 2013. Available at <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f5070a92-96b8-476a-a2dc-18b22d95e5e0>. Accessed August 28, 2013.
5. Rixubis [prescribing information]. Westlake Village, Ca: Baxter Healthcare Corporation; 2013. Available at http://rixubis.com/pdf/rixubis_pi.pdf. Accessed August 29, 2013.
6. Windyga J, Lissitchkov T, Stasyhyn O, Mamonov V, Rusen L, Lamas JL, et al. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicenter phase I/III study in previously treated patients with severe (FIX level < 1%) or moderately severe (FIX level \leq 2) hemophilia B. *Haemophilia* 2013;1-10.
7. Roth DA, Kessler CM, Pasi J, Rup B, Courter SG, Tubridy KL. Human recombinant factor IX: safety and efficacy studies in hemophilia B patients previously treated with plasma-derived factor IX concentrates. *Blood* 2001;98(13):3600-3606.

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