Medical Drug Clinical Criteria

Subject:	Agents for Hemophilia B		
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Overview

This document addresses select agents for hereditary or congenital hemophilia B, also called factor IX (FIX) deficiency or Christmas disease. This document does not address fibrin products, fibrin sealants and blood products provided by blood banks, nor does it address acquired hemophilia B, which is a very rare autoimmune disorder, and not a congenital disease, that requires highly individualized treatment. Bypassing agents (i.e., NovoSeven RT, FEIBA, and SevenFact) for those who develop antibodies or inhibitors to factor products are discussed in another document.

Factor replacement treatments can be created from blood products (human plasma-derived) and others that are manufactured (recombinant). Replacement therapy may be given on a routine, preventive basis which is also called prophylactic therapy. The infusion of factor replacements given to stop a bleeding episode is called on-demand or episodic therapy.

Products in this document include:

- Coagulation Factor IX, Human plasma-derived
  - Alphanine SD, Mononine
- Factor IX Complex, human plasma-derived
  - Profilnine SD
- Factor IX Recombinant
  - Benefix, Ixinity, Rixubis
- Coagulation Factor IX-Long-Acting
  - Recombinant, Albumin Fusion Protein--- Idelvion
  - Recombinant coagulation factor IX, Fc Fusion Protein --- Alprolix
  - Recombinant coagulation factor IX, GlycoPEGylated --- Rebinyn

Hereditary hemophilia B is the second most common type of hemophilia after hemophilia A (four times less common than hemophilia A). Although it is usually inherited, about one third of cases are caused by spontaneous mutations. Hemophilia A and B are clinically indistinguishable from one another, except by factor analysis. Hemophilia B is related to mutations in the gene coding for coagulation Factor IX (CDC 2014).

The World Federation of Hemophilia (Srivastava, 2020) and International Society on Thrombosis and Haemostasis (ISTH) (Rezende 2024) both note there is a relationship of bleeding severity to the clotting factor level. Mild disease is identified as a clotting factor level of >5-40 IU/dl or 5 to < 40% of normal. A bleeding episode for individuals with mild risk includes severe bleeding with major trauma or surgery. Individuals with 1-5 IU/dl or 1-5% of normal are considered “moderate” risk for occasional spontaneous bleeding and prolonged bleeding with minor trauma or surgery (Srivastava, 2020). Severe hemophilia is defined as a clotting factor level < 1 IU/dl or < 1% of normal.

Hemophilia severity:

- Severe hemophilia – Severe hemophilia is defined as < 1 percent factor activity, which corresponds to < 1 IU/dL.
- Moderate hemophilia – Moderate hemophilia is defined as a factor activity level ≥ 1 percent of normal and ≤ 5 percent of normal, corresponding to ≥ 1 and ≤ 5 IU/dL.
- Mild hemophilia – Mild hemophilia is defined as a factor activity level > 5 percent of normal but < 40 percent of normal (> 5 and < 40 IU/dL).

World Federation of Hemophilia 2020 Guidelines for treatment of hemophilia state that prophylaxis prevents bleeding and joint destruction and that prophylaxis should enable those with hemophilia to lead healthy and active lives. The updated 2020 guidelines proposes that the definition of prophylaxis be based on outcomes rather than doses or timing of initiation, and treatment regimens that take into account the hemophilic phenotype of the individual in addition to factor levels. The WFH 2020 guidelines have been endorsed

by several societies worldwide, including the U.S. NHF. ISTH 2024 guidelines recommend prophylactic treatment for anyone with moderate to severe disease as defined by endogenous factor activity. Short-term prophylaxis (of 4 to 8 weeks) may interrupt the bleeding cycle and benefit individuals with repeated bleeding into target joints. Prophylaxis does not reverse existing joint damage but reduces bleeding and may slow progression of joint damage. Prophylactic clotting factor administration is recommended prior to the individual engaging in activities with higher risk of injury. Randomized trials of prophylactic therapy of hemophilia have demonstrated a decreased incidence of arthropathy (Gringeri, 2011; Manco-Johnson, 2007).

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Alphanine SD or Mononine (Human plasma-derived, Coagulation Factor IX)

Initial requests for Alphanine SD or Mononine (Human plasma derived, Coagulation Factor IX) may be approved if the following criteria are met:

I. Individual has a diagnosis of hemophilia B (also called factor IX deficiency or Christmas disease); **AND**
II. Individual is using for the treatment of bleeding episodes;

OR

III. Individual has a diagnosis of moderate to severe hemophilia B (defined as 5 IU/dL or less endogenous Factor IX) (Rezende 2024); **AND**
IV. Individual is using for routine prophylaxis to prevent or reduce the frequency of bleeding episodes;

OR

V. Individual has a diagnosis of mild hemophilia B (defined as endogenous Factor IX less than 40 IU/dL [less than 40%], but greater than 5 IU/dL) (NHF, Srivastava 2020); **AND**
VI. Individual is using for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; **AND**
VII. Individual has one of the following:
  A. One or more episodes of spontaneous bleeding into joint; **OR**
  B. One or more episodes severe, life-threatening, or spontaneous bleeding as determined by prescriber; **OR**
  C. Severe phenotype hemophilia determined by the individual's risk factors that increase the risk of a clinically significant bleed, including but not limited to, participation in activities likely to cause injury/trauma, procoagulant and anticoagulant protein levels, comorbid conditions affecting functional ability and physical coordination, or history of a clinically significant bleed.

Continuation requests for Alphanine SD or Mononine (Human plasma derived, Coagulation Factor IX) may be approved if the following criteria are met:

I. Individual has a diagnosis of hemophilia B; **AND**
II. Individual has had a positive therapeutic response to treatment (for example, reduction in frequency and/or severity of bleeding episodes).

Alphanine SD or Mononine (Human plasma derived, Coagulation Factor IX) may not be approved for the following:

I. Treatment or reversal of coumarin-induced anticoagulation; **OR**
II. Hemorrhagic state or coagulopathy associated with liver dysfunction; **OR**
III. Treatment of individuals with hemophilia A with inhibitors to factor VIII; **OR**
IV. Replacement therapy of other clotting factors which include factors II, VII, and X; **OR**
V. When the above criteria are not met and for all other indications.

Profilnine SD (Human plasma-derived, Factor IX Complex)

Initial requests for Profilnine SD (Human plasma-derived, Factor IX Complex) may be approved if the following criteria are met:

I. Individual has a diagnosis of hemophilia B (also called-factor IX deficiency or Christmas disease); **AND**
II. Individual is using for the treatment of bleeding episodes;

OR

III. Individual has a diagnosis of moderate to severe hemophilia B (defined as 5 IU/dL or less endogenous Factor IX) (Rezende 2024); **AND**
IV. Individual is using as routine prophylaxis to prevent or reduce the frequency of bleeding episodes;

OR

V. Individual has a diagnosis of mild hemophilia B (defined as endogenous Factor IX less than 40 IU/dL [less than 40%], but greater 5 IU/dL) (NHF, Srivastava 2020); **AND**
VI. Individual is using for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; **AND**
VII. Individual has one of the following:
   A. One or more episodes of spontaneous bleeding into joint; **OR**
   B. One or more episodes of severe, life-threatening, or spontaneous bleeding as determined by the prescriber; **OR**
   C. Severe phenotype hemophilia determined by the individual's risk factors that increase the risk of a clinically significant bleed, including but not limited to, participation in activities likely to cause injury/trauma, procoagulant and anticoagulant protein levels, comorbid conditions affecting functional ability and physical coordination, or history of a clinically significant bleed.

Continuation requests for Profilnine SD (Human plasma-derived, Factor IX Complex) may be approved if the following criteria are met:

I. Individual has a diagnosis of hemophilia B; **AND**
II. Individual has had a positive therapeutic response to treatment (for example, reduction in frequency and/or severity of bleeding episodes).

Profilnine SD (Human plasma-derived, Factor IX Complex) may not be approved for the following:

I. Individual has a diagnosis of Factor VII deficiency; **OR**
II. When the above criteria are not met and for all other indications.

Benefix, Ixinity, or Rixubis (Recombinant Factor IX)

Initial requests for Benefix, Ixinity, or Rixubis (Recombinant Factor IX) may be approved if the following criteria are met:

I. Individual has a diagnosis of hemophilia B~~,~~ (also called factor IX deficiency or Christmas disease); **AND**
II. Individual is using for one of the following:
   A. The treatment of bleeding episodes; **OR**
   B. Peri-procedural management for surgical, invasive or interventional radiology procedures;

OR

III. Individual has a diagnosis of moderate to severe hemophilia B (defined as 5 IU/dL or less endogenous Factor IX) (Rezende 2024); **AND**
IV. Individual is using as routine prophylaxis to prevent or reduce the frequency of bleeding episodes;

OR

V. Individual has a diagnosis of mild hemophilia B (defined as endogenous Factor IX less than 40 IU/dL [less than 40%], but greater than 5 IU/dL) (NHF, Srivastava 2020); **AND**
VI. Individual is using for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; **AND**
VII. Individual has one of the following:
   A. One or more episodes of spontaneous bleeding into joint; **OR**
   B. One or more episodes of severe, life-threatening, or spontaneous bleeding as determined by the prescriber; **OR**
   C. Severe phenotype hemophilia determined by the individual's risk factors that increase the risk of a clinically significant bleed, including but not limited to, participation in activities likely to cause injury/trauma, procoagulant and anticoagulant protein levels, comorbid conditions affecting functional ability and physical coordination, or history of a clinically significant bleed.

Continuation requests for Benefix, Ixinity, Rixubis (Recombinant Factor IX) may be approved if the following criteria are met:

I. Individual has a diagnosis of hemophilia B; **AND**
II. Individual has had a positive therapeutic response to treatment (for example, reduction in frequency and/or severity of bleeding episodes).

Benefix, Ixinity, Rixubis (Recombinant Factor IX) may not be approved for the following:

I. Treatment of other factor deficiencies (for example factors II, VII, VIII and X); **OR**
II. Treatment of individuals with hemophilia A with inhibitors to factor VIII; **OR**
III. To reverse coumarin-induced anticoagulation; **OR**
IV. Treatment of bleeding due to low levels of liver-dependent coagulation factors; **OR**
V. Using for the induction of immune tolerance in individuals with hemophilia B; **OR**
VI. When the above criteria are not met and for all other indications.

Idelvion (Recombinant Long-Acting, Albumin Fusion Protein Coagulation Factor IX), Alprolix (Recombinant, Fc Fusion Protein Coagulation Factor IX), or Rebinyn (Recombinant, glycoPEGylated Coagulation Factor IX)

Initial requests for Idelvion (Recombinant Long-Acting, Albumin Fusion Protein Coagulation Factor IX), Alprolix (Recombinant, Fc Fusion Protein Coagulation Factor IX), or Rebinyn (Recombinant, glycoPEGylated Coagulation Factor IX) may be approved if the following criteria are met:

I. Individual has a diagnosis of moderate to severe hemophilia B (also called factor IX deficiency or Christmas disease); **AND**
II. Individual has 5 IU/dL or less endogenous Factor IX (Rezende 2024); **AND**
III. Individual is using for one of the following:
    A. The treatment of bleeding episodes; **OR**
    B. Peri-procedural management for surgical, invasive or interventional radiology procedures; **OR**
    C. Routine prophylaxis to prevent or reduce the frequency of bleeding episodes;

OR

IV. Individual has a diagnosis of mild to moderate hemophilia B; **AND**
V. Individual has endogenous Factor IX level less than 40 IU/dL (less than 40%) but greater than or equal to 1 IU/dL (NHF, Srivastava 2020); **AND**
VI. Individual is using for one of the following:
    A. Individual is using for the treatment of bleeding episodes; **OR**
    B. Individual is using for peri-procedural management for surgical, invasive or interventional radiology procedures; **OR**
    C. Individual is using for routine prophylaxis to prevent or reduce the frequency of bleeding episodes for one of the following:
        1. Individual has had one or more episodes of spontaneous bleeding into joint; **OR**
        2. Individual has had one or more episodes of severe, life-threatening, or spontaneous bleeding as determined by the prescriber; **OR**
        3. Severe phenotype hemophilia determined by the individual's risk factors that increase the risk of a clinically significant bleed, including but not limited to, participation in activities likely to cause injury/trauma, procoagulant and anticoagulant protein levels, comorbid conditions affecting functional ability and physical coordination, or history of a clinically significant bleed.

Continuation requests for Idelvion (Recombinant Long-Acting, Albumin Fusion Protein Coagulation Factor IX), Alprolix (Recombinant, Fc Fusion Protein Coagulation Factor IX), or Rebinyn (Recombinant, glycoPEGylated Coagulation Factor IX) may be approved if the following criteria are met:

I. Individual has a diagnosis of hemophilia B; **AND**
II. Individual has had a positive therapeutic response to treatment (for example, reduction in frequency and/or severity of bleeding episodes).

Idelvion (Recombinant Long-Acting, Albumin Fusion Protein Coagulation Factor IX), Alprolix (Recombinant, Fc Fusion Protein Coagulation Factor IX), or Rebinyn (Recombinant, GlycoPEGylated Coagulation Factor IX) may not be approved for the following:

I. Using for the induction of immune tolerance in individuals with hemophilia B; **OR**
II. When the above criteria are not met and for all other indication.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Coagulation Factor IX, Human plasma-derived (Alphanine SD, Mononine)

HCPCS	
J7193	Factor IX (Anti-hemophilic factor, purified, non-recombinant) per IU [AlphaNine SD, Mononine]
ICD-10 Diagnosis	
D67	Hereditary factor IX deficiency [hemophilia B]
D68.311	Acquired hemophilia
Z29.89	Encounter for other specified prophylactic measure
Z79.899	Other long term (current) drug therapy [prophylactic]

Factor IX Complex Human (Profilnine SD)

HCPCS

J7194	Factor IX complex, per IU [Profilnine SD]

ICD-10 Diagnosis

D67	Hereditary factor IX deficiency [hemophilia B]
Z29.89	Encounter for other specified prophylactic measure
Z79.899	Other long term (current) drug therapy [prophylactic]

Factor IX Recombinant (Benefix, Ixinity, Rixubis)

HCPCS

J7195	Injection, factor IX (Anti-hemophilic factor, recombinant) per IU, not otherwise specified [Benefix, Ixinity]
J7200	Injection, factor IX, (Anti-hemophilic factor, recombinant), Rixubis, per IU
J7213	Injection, coagulation factor ix (recombinant) [Ixinity], 1 IU

ICD-10 Diagnosis

D67	Hereditary factor IX deficiency [hemophilia B]
D68.311	Acquired hemophilia
Z29.89	Encounter for other specified prophylactic measure
Z79.899	Other long term (current) drug therapy [prophylactic]

Coagulation Factor IX—Long Acting Recombinant, Albumin Fusion Protein (Idelvion); Recombinant Coagulation Factor IX, Fc Fusion Protein (Alprolix); Recombinant Coagulation Factor IX, GlycoPEGylated (Rebinyn)

HCPCS

J7201	Injection, factor IX, Fc fusion protein (recombinant), Alprolix, 1 IU
J7202	Injection, factor IX, albumin fusion protein, (recombinant), Idelvion, 1 IU
J7203	Injection factor ix, (antihemophilic factor, recombinant), glycopegylated, (rebinyn), 1 IU

ICD-10 Diagnosis

D67	Hereditary factor IX deficiency [hemophilia B]
D68.311	Acquired hemophilia
Z29.89	Encounter for other specified prophylactic measure
Z79.899	Other long term (current) drug therapy [prophylactic]

Document History

Revised: 11/15/2024
Document History:

- 04/04/2025 – Coding Update: Removed ICD-10-CM Z29.8 and replaced with Z29.89 for AlphaNine SD, Mononine, Profilnine SD, Benefix, Ixinity, Rixubis, Idelvion, Alprolix, and Rebinyn.
- 11/15/2024 – Annual Review: add indication to continuation criteria, add moderate disease for prophylaxis. Coding Reviewed: No changes.
- 11/17/2023 – Annual Review: No changes. Coding Reviewed: No changes.
- 11/18/2022 – Annual Review: Consolidate Ixinity with Benefix and Rixubis criteria, Allow Rebinyn for prophylaxis, modify prophylaxis criteria, wording, and formatting changes. Coding Reviewed: No changes. Effective 7/1/2023 Added HCPCS J7213 for Ixinity.
- 05/20/2022 – Administrative update to remove documentation.
- 11/19/2021 – Annual Review: Remove obsolete agent Bebulin from document. Add continuation criteria for all agents. Coding Review: Removed Bebulin from HCPCS J7194.
- 08/01/2021 – Administrative update to add documentation.
- 11/20/2020 – Annual Review: Update Factor IX Human Plasma-derived and Recombinant agents to allow for prophylactic use in those with mild to moderate disease with severe phenotype hemophilia per guidelines. Update criteria to restrict use of Benefix for induction of immune tolerance per label. Updated references. Wording and formatting changes. Coding Reviewed: Added ICD-10-CM D68.311 to Human Plasma and Recombinant agents.

- 11/15/2019 – Annual Review: Create new clinical criteria document for agents for hemophilia B (Alphanine SD, Mononine, Bebulin, Profilnine SD, Benefix, Ixinity, Rixubis, Idelvion, Alprolix, Rebinyn removed from ING-CC-0065). Clarified other names for hemophilia B. Wording and formatting changes for clarity and consistency. Coding Reviewed: No changes.

References

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.