Reference number(s)
4848-A

STANDARD MEDICARE PART B MANAGEMENT

PROFILNINE (factor IX complex [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Hemophilia B

B. Compendial Uses
1. Bleeding due to low levels of liver-dependent coagulation factors
2. Factor II deficiency
3. Factor X deficiency
4. Drug toxicity, anticoagulant

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Hemophilia B
Authorization of 12 months may be granted for treatment of hemophilia B.

B. Bleeding due to low levels of liver-dependent coagulation factors
Authorization of 12 months may be granted for treatment of bleeding due to low levels of liver-dependent coagulation factors.

C. Factor II deficiency
Authorization of 12 months may be granted for treatment of factor II deficiency.

D. Factor X deficiency
Authorization of 12 months may be granted for treatment of factor X deficiency.

E. Anticoagulation reversal
Authorization of 1 month may be granted for anticoagulation reversal.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. Anticoagulation Reversal
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. All Other Indications
Authorization for 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication
2. The requested medication is being used to treat an indication enumerated in Section II
3. The member is receiving benefit from therapy (e.g., reduced frequency or severity of bleeds).

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Profilnine.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Profilnine are covered in addition to the following:
1. Bleeding due to low levels of liver-dependent coagulation factors
2. Factor II deficiency
3. Factor X deficiency
4. Drug toxicity, anticoagulant

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Profilnine to treat bleeding due to low levels of liver-dependent coagulation factors can be found in a study of 30 patients by Gazzard and colleagues. Factor IX was at least as effective as fresh frozen plasma in the treatment of clotting factor deficiency secondary to severe liver disease. In a comparison of the two agents in 30 patients with chronic liver disease, all patients had prothrombin times that were prolonged 4 seconds or more and were to undergo percutaneous needle liver biopsy. The first 15 patients were given 600 mL fresh frozen plasma over 30 minutes, followed by 300 mL 6 hours later. The second 15 patients were given 20 mL of factor IX complex containing 2000 units of factors II, IX, and X. Vital signs and signs of bleeding were monitored for 24 hours post-biopsy; packed cell volume and coagulation studies were performed. Although there was no evidence of bleeding in any patient, only 3 of 15 patients receiving fresh frozen plasma had a normal prothrombin time after biopsy, and in 7 of the 15 patients receiving factor IX, the prothrombin time was within normal limits 30 minutes after receiving the dose. Serum levels of clotting factors increased to above

10% of normal in all 30 patients, and were still increased 24 hours post-dosing. No thrombotic sequelae were reported.

Support for using Profilnine to treat factor II deficiency can be found in the guideline posted by the National Bleeding Disorders foundation. Profilnine is a human plasma-derived prothrombin complex concentrate recommended for use in patients with factor II deficiency.

Support for using Profilnine to treat factor X deficiency can be found in a case report by Kouides and Kulzer. An 18-year-old male with severe factor X deficiency (level less than 1%) successfully used home-infusion prophylactic treatment with factor IX (Profilnine(R)) to overcome epistaxis and joint bleeding. Prior to initiation of the prophylactic regimen, the patient was treated on demand from 3 to 14 times a year. Nose bleeds were most common, followed by joint bleeds and hematomas (the result of trauma). His factor IX protocol was 30 units/kg twice a week at least 3 days apart. If breakthrough bleeding occurred, he was to infuse another dose. He was instructed not to infuse more than 2 doses in 24 hours or to receive infusions on more than 3 consecutive days. During the initial 12 months of prophylactic therapy, no breakthrough bleeding occurred. During an additional 11 months of therapy, he reported one bleeding episode that was the result of trauma. His quality of life improved after starting this protocol. He had no absences from school due to bleeding; he was able to participate in recreational basketball and track. No thrombotic events occurred. A trough level measured at 48 hours after factor IX infusion showed a factor X level of 30% (minimum hemostatic level 10% to 20%).

Support for using Profilnine to treat drug toxicity due to anticoagulant can be found in a retrospective chart review by Safaoui et al. A retrospective chart review revealed that Factor IX complex in combination with traditional therapy achieved rapid reversal of warfarin-induced coagulopathy in patients with intracranial hemorrhage (n=28). Adult patients (mean age 78.2 years (yr); range, 55 to 94 yr; 50% male) were divided into 1 of 2 groups based on the time from presentation to administration of Factor IX complex, 60 minutes or less (group 1) or more than 60 minutes (group 2). All patients received Factor IX complex 2000 units. Patients with an INR greater than 3 at 10 minutes after Factor IX complex infusion received a repeat dose. Vitamin K 10 mg IV or subQ was administered to 82% (23 of 28) of patients and 96% (27 of 28) of patients received fresh frozen plasma. The mean INR at presentation for group 1 was 5.8 +/- 8.6, which significantly reduced to 2.2 +/- 0.76 (p=0.005) after treatment. Similarly, the mean INR at presentation for group 2 was 4.7 +/- 3.2, which significantly reduced to 1.8 +/- 0.73 (p=0.001) after treatment. Of 11 patients with an INR obtained within 30 minutes of Factor IX complex infusion, the mean time to INR correction was 13.5 minutes (min). For all patients, the mean time to INR correction was 116 min. At 24 hours, reversal of warfarin-induced coagulopathy remained significant 1.8 +/- 0.87 (p=0.012) and 1.2 +/- 0.28 (p=0.001) in group 1 and 2, respectively. No early thrombotic or allergic events were reported. Fatalities occurred in 10 patients designated as do not resuscitate. Additionally, a retrospective chart review by Siddiq and colleagues found factor IX complex concentrate in combination with fresh frozen plasma and vitamin K (n=10) may be a more effective alternative than fresh frozen plasma (FFP) and vitamin K alone (n=9) for rapid reversal of warfarin-induced coagulopathy in patients with intracranial hemorrhage. Consecutive patients received either Factor IX complex concentrate 25 units/kg (INR less than 4) or 50 units/kg (INR greater than 4) IV push over 2 to 5 minutes in combination with vitamin K 10 mg IV infusion over 30 minutes and FFP 10 to 15 mL/kg (age 67.2 +/- 18.51 years (yr); 50% male) or FFP and vitamin K alone (76.89 +/- 18.5 yr; 56% male). INR was monitored upon presentation and approximately every 3 hours (hr) thereafter until a target INR of 1.4 or less was met. The mean INR at presentation was 2.44 +/- 1.48 for the Factor IX complex concentrate group and 1.84 +/- 0.31 for the FFP-vitamin K alone group. Both treatments significantly reduced INR to target level. The mean INR was reduced to 1.34 +/- 0.07 (p less than 0.005) in the Factor IX complex concentrate group and 1.34 +/- 0.08 (p less than 0.05) in the FFP-vitamin K alone group. However, 80% of patients (8 of 10) met the target INR within 3 to 4 hr of treatment initiation in the Factor IX complex concentrate group compared with 33% (3 of 9) in the FFP-vitamin K alone group (p=0.012). The mean time required to correct INR was significantly less in the Factor IX complex concentrate group 4.25

+/- 2.12 hr compared with the FFP-vitamin K alone group 8.52 +/- 5.6 hr (p less than 0.05). No treatment complications were observed.

VI. REFERENCES

1. Profilnine [package insert]. Los Angeles, CA: Grifols Biologicals LLC; March 2021.
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4. Gazzard BG, Henderson JM, & Williams R: The use of fresh frozen plasma or a concentrate of factor IX as replacement therapy before liver biopsy. Gut 1975; 16:621-625.
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6. Safaoui MN, Aazami R, Hotz H, et al: A promising new alternative for the rapid reversal of warfarin coagulopathy in traumatic intracranial hemorrhage. Am J Surg 2009; 197(6):785-790.
7. Siddiq F , Jalil A , McDaniel C , et al: Effectiveness of Factor IX complex concentrate in reversing warfarin associated coagulopathy for intracerebral hemorrhage. Neurocrit Care 2008; 8(1):36-41.