Reference number(s)
4799-A

STANDARD MEDICARE PART B MANAGEMENT

NOVOSEVEN RT (coagulation factor VIIa [recombinant])

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 Indications
1. Hemophilia A or hemophilia B with inhibitors
2. Congenital factor VII deficiency
3. Glanzmann's thrombasthenia
4. Acquired hemophilia

B. Compendial Uses
1. Acquired von Willebrand syndrome
2. Inhibitors to factor XI
3. Drug action reversal, anticoagulation
4. Postoperative hemorrhage, cardiac surgery

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. Congenital Factor VII Deficiency
Authorization of 12 months may be granted for treatment of congenital factor VII deficiency.

B. Hemophilia A with Inhibitors
Authorization of 12 months may be granted for treatment of hemophilia A with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or the member has a history of an inhibitor titer ≥ 5 BU.

C. Hemophilia B with Inhibitors
Authorization of 12 months may be granted for treatment of hemophilia B with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL) or the member has a history of an inhibitor titer ≥ 5 BU.

D. Glanzmann's Thrombasthenia
Authorization of 12 months may be granted for treatment of Glanzmann's thrombasthenia.

E. Acquired Hemophilia
Authorization of 12 months may be granted for treatment of acquired hemophilia.

F. Acquired von Willebrand Syndrome
Authorization of 12 months may be granted for treatment of acquired von Willebrand syndrome when other therapies failed to control the member's condition (e.g., desmopressin or factor VIII/von Willebrand factor).

G. Inhibitors to Factor XI
Authorization of 12 months may be granted for treatment of inhibitors to factor XI.

H. Anticoagulation Reversal
Authorization of 1 month may be granted for emergency reversal of anticoagulation.

I. Postoperative Hemorrhage following Cardiac Surgery
Authorization of 1 month may be granted for treatment of postoperative hemorrhage following cardiac surgery.

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. Postoperative Hemorrhage following Cardiac Surgery
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

C. 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. APPENDIX

Appendix: Inhibitors - Bethesda Units (BU)
The presence of inhibitors is confirmed by a specific blood test called the Bethesda inhibitor assay.

- High-titer inhibitors:
  - ≥ 5 BU/mL
  - Inhibitors act strongly and quickly neutralize factor
- Low-titer inhibitors:
  - < 5 BU/mL
  - Inhibitors act weakly and slowly neutralize factor

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Novoseven RT.
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
3. WFH Guidelines for the Management of Hemophilia, 3rd edition
4. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders
5. World Federation of Hemophilia. Platelet function disorders
6. Use of recombinant activated factor VII in patients with Glanzmann's thrombasthenia: a review of the literature.
7. Congenital factor XI deficiency: an update.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Novoseven RT are covered in addition to the following:

1. Acquired von Willebrand syndrome
2. Inhibitors to factor XI
3. Drug action reversal, anticoagulation
4. Postoperative hemorrhage, cardiac surgery

VI. EXPLANATION OF RATIONALE

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

Support for using NovosevenRT to treat acquired von Willebrand syndrome can be found in a study by Tiede et al. Use of recombinant factor VIIa has been reported in AVWS and in von Willebrand disease patients, particularly those who develop alloantibodies against VWF. It is usually administered with a dose of 90 µg/kg (range, 40-150 µg/kg) and for a median of 3 doses (range, 1-54 doses). Treatment is usually effective with responses reported in 96% of patients. Adverse events appear to be uncommon; myocardial infarction was reported in one patient with type 2A von Willebrand disease. The rate of thromboembolic complications is low in hemophilia patients receiving recombinant factor VIIa, but it is currently unknown whether this is holds for patients with AVWS or von Willebrand disease. Caution should be exerted, particularly in elderly patients and those at risk of thromboembolism.

Support for using Novoseven RT to treat inhibitors to factor XI can be found in several articles.
Duga and Salomon state the treatment of factor XI deficiency is difficult because factors influencing bleeding risks are still unknown. The use of lower doses of recombinant activated factor VII in comparison with the doses commonly applied in hemophilia A or B seems promising also when assessed in vitro by thrombin generation test.
Individuals with severe factor XI deficiency who have developed a factor XI inhibitor may not have an increase in factor XI with factor XI replacement products and may require treatment with a bypassing agent such as recombinant activated factor VII (recombinant factor VIIa; rFVIIa). In their review, Roberts et al (2004) state recombinant VIIa has also been used to treat patients with factor XI deficiency either with or without inhibitors

to factor XI. Doses of 90 to 120 µg/kg every 2 to 3 hours until bleeding ceases have been found to be effective in this condition, but the optimal dose has not been clearly defined. Some investigators now consider rfVIIa to be the treatment of choice in factor XI deficiency and for inhibitors to factor XI (Roberts 2004).

Support for using Novoseven RT to reverse the effects of anticoagulants can be found in a study by Ingerslev, Vanek and Culic. Activated recombinant factor VII (rFVIIa) was beneficial for patients requiring emergency anticoagulation reversal in a database review of an international, internet-based registry (n=18). Patients who received rFVIIa as rescue treatment for bleeding during or after a surgical or invasive procedure, who had verifiable results and provider consent were included. The anticoagulants utilized, which required reversal included low-molecular-weight heparin (n=6), unfractionated heparin (n=8), coumarin (n=3) and warfarin (n=1). All but 1 patient received a single dose of rFVIIa. The median dose was 87.35 micrograms/kilogram (mcg/kg) (range, 20 to 106 mcg/kg). The primary outcome was cessation of hemorrhage. Cessation of hemorrhage was achieved in 10 patients. A marked reduction in hemorrhage occurred in 5 patients and a considerable slowing of hemorrhage occurred in 3 patients. Neither the severity of initial bleeding nor the dose of rFVIIa seemed to influence efficacy. The need for blood products (packed red blood cells, whole, blood, fresh frozen plasma, cryoprecipitate or platelets) or fluid therapy (crystalloids or colloids) from 24 hours before to 24 hours after treatment significantly improved (p less than 0.001 and p less than 0.05, respectively). No adverse effects were reported and rFVIIa was considered well tolerated. Of the 18 patients, 14 had reported final outcomes: 8 were discharged, 1 stayed in the ICU, and 5 fatalities occurred but were not attributed to rFVIIa.
Ilyas and colleagues completed a retrospective, cohort-controlled database review of elderly patients with intracranial hemorrhage (n=54). Elderly patients treated with warfarin, who presented with a new or developing intracranial bleed and an international normalized ratio (INR) greater than 1.4 received rFVIIa 10 to 100 micrograms/kilogram (mcg/kg) (n=24; age 76.5 +/- 11 years (yr); 50% male). Demographics of the historical controls was similar (n=30; age 76.4 +/- 12.4 yr; 63% male). Patients treated with rFVIIa rapidly achieved INR reduction to 1.3 or less compared with historical controls, 2.4 +/- 1.5 hours (hr) vs 13.7 +/- 15.6 hr, respectively, and INR remained corrected for an average of 12.2 +/- 8.8 hr. Patients treated with rFVIIa required noticeably less plasma for hemostasis compared with historical controls 4 +/- 3 units vs 7.7 +/- 4.4 units, respectively. A dose-response effect in duration of INR correction was observed: 3 hr INR correction with rFVIIa 1.2 milligrams (mg), 13 hr INR correction with 2.4 to 4.8 mg, and 17 hr INR correction for doses greater than 4.8 mg. Most patients received vitamin K 10 mg IV within the first 12 hours of treatment. One patient experienced a myocardial infarction that was temporally related to rFVIIa administration but fully recovered. A study limitation is the retrospective study design.

Support for using Novoseven RT to treat postoperative hemorrhage after cardiac surgery can be found in a meta-analysis by Ponschab et al. In a meta-analysis of 6 clinical trials (2 randomized, 3 propensity matched, and 1 case matched) (n=470), using recombinant activated factor VII (rFVIIa) (18 mcg/kg to 70 mcg/kg given in repeatable doses, and 90 mcg/kg given as a single dose) in post-cardiac surgery patients did not significantly reduce the rate of surgical reexploration (13% vs 42% in the rFVIIa and control groups, respectively) (odds ratio (OR) 0.27; 95% confidence interval (CI) 0.04 to 1.9; p=0.19), and was associated with an increased rate of stroke (4.7% vs 0.9% in the rFVIIa and control groups, respectively) (OR 3.69; 95% CI 1.1 to 12.38; p=0.03). Incidence in overall perioperative vascular events (myocardial infarction, stroke, and DVT) (7.5% vs 5.6% in the rFVIIa and control groups, respectively) (OR 1.84; 95% CI 0.82 to 4.09; p=0.14), and mortality (13% vs 12% in the rFVIIa and control groups, respectively) (OR 1.14; 95% CI 0.65 to 2.01) was not different between the groups. All 6 studies reported reduction in blood loss with rFVIIa; however, due to the different methods of measurement, the results could not be compared between the studies.
Additionally, the use of recombinant activated factor VII (rFVIIa) in patients who bleed after cardiac surgery was effective in a phase II, multicenter, randomized, double-blind, placebo-controlled trial (n=172); however, however, the incidence of serious adverse events was higher in the rFVIIa group (Gill et al). Patients who were bleeding after cardiac surgery requiring cardiopulmonary bypass (CPB) and needing conventional transfusion therapy or surgical reexploration were randomized to receive placebo (n=68), 40 micrograms per kilogram

(mcg/kg) rFVIIa (n=35), or 80 mcg)/kg rFVIIa (n=69). The study reported that rFVIIa reduced bleeding and patients receiving rFVIIa had significantly fewer reoperations (p=0.03) (placebo, 25%; 40 mcg/kg, 14%; 80 mcg/kg 12%), and less transfusion requirements compared with patients receiving placebo (p=0.01). The primary end point of the study was the number of patients experiencing serious adverse events (SAEs), and the results showed that there were more SAEs (death, acute myocardial infarction, cerebral infarction, pulmonary embolus and other thrombotic events) in the rFVIIa groups than in the placebo group; however, the differences were not statistical significant (placebo, 7%; 40 mcg/kg, 14%; p=0.25; 80 mcg/kg, 12%; p=0.43). There was a total of 14 deaths, with 6% of the placebo group and 10% of the combined rFVIIa dose groups. The major limitation of the study was its small sample size with some of the patients who received rFVIIa were older, were on CPB longer, and received more transfusions before randomization. These factors were strong predictors of the SAEs and mortality and may partially account for its increased number (although statistically insignificant) in rFVIIa-treated patient.

VII. REFERENCES

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