KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Recombinant Activated Factor VII (NovoSeven®)

- Glanzmann's Disease
- Hemophilia
- Post-Partum Hemorrhage
- Cardiac Surgery Hemorrhage

Criteria

For Non-Medicare Members

Kaiser Permanente has elected to use the Coagulation Factor VIIa – (NovoSeven) (KP-0452) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

***MCG Manuals are proprietary and cannot be published and/or distributed.** However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Last 12 months of clinical notes from requesting provider &/or specialist (hematology, primary care physician)

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Glanzmann's disease (aka Glanzmann's thrombasthenia) is a platelet disorder characterized by a deficiency in the platelet membrane glycoproteins (GP) IIb-IIIa. It is one of several hereditary platelet disorders typified by normal platelet numbers and a prolonged bleeding time. NovoSeven® may also be appropriate for use with patients who have other bleeding disorders such as Glanzmann's thrombasthenia or Bernard-Soulier's thrombasthenia.

NovoSeven® (manufactured by Novo Nordisk, Denmark) is a product containing recombinant coagulation Factor VII. It has been used to prevent bleeding and treat hemorrhage during surgery in patients with hemophilia A with a Factor VIII inhibitor, hemophilia B with a Factor IX inhibitor and acquired deficiencies in Factors VIII or IX.

NovoSeven® has been approved by the FDA as a biological product.

People with hemophilia A (approximately 85% of hemophilia patients) lack the blood clotting protein, factor VIII and people with hemophilia B lack factor IX. The severity of the condition varies, depending on the amount of clotting factor in the blood. About 70% of individuals with hemophilia A have less than 1 percent of the normal amount of clotting factor and are considered to have severe disease. Treatment of hemophilia A or B consists of replacement of the deficient factor.

Back to Top

Approximately 20-50% of severe hemophilia A patients and 1.5-3% of hemophilia B patients (Kulkarni, 2001) develop antibodies called inhibitors that block the activity of the replacement clotting factor. Management of hemophilia patients with inhibitors is challenging. Injection of high quantities of clotting factors is sometimes effective at neutralizing the inhibitors and allowing sufficient quantities of the factors to circulate. Another treatment is injection of porcine factor VIII, which is often sufficiently different from human factor VIII to go unrecognized by inhibitors. However, many patients have cross-reactive antibodies to Porcine FVIII concentrates. Removing the antibody from the plasma (plasmapheresis), in combination with injections of clotting factor, is sometimes used.

Another approach to treatment is the use of bypassing agents, treatments that induce hemostasis independent of the presence of factors VIII and IV. Prothrombin complex concentrates (PCCs) and activated prothrombin complex concentrates (aPCC) were developed in the 1970s. They are derived from human plasma and contain the vitamin K-dependent coagulation proteins.

Recombinant activated Factor VII (rFVIIa) or NovoSeven is also a bypassing agent. This product is derived from cultured baby hamster kidney cells using recombinant DNA technology. Because it does not any human serum or proteins, NovoSeven has a low risk of infecting patients with human viruses that could be present in plasma-derived products. NovoSeven has a relatively short half-life and injections must be given frequently. The initial recommended dose is 90 ug/kg every two hours until cessation of bleeding. PCCs and aPCCs have been associated with thromboembolic side effects and it is also possible that there is a risk of thrombosis with NovoSeven (Kulkarni, 2001).

NovoSeven (manufactured by Novo Nordisk, Denmark) has been available in the European Union since 1996. In 1999, NovoSeven was approved by the FDA for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factors VIII or IX. It is available in the US through Novo Nordisk Pharmaceuticals, New Jersey.

Major bleeding is a common and potentially serious complication in high-risk **cardiovascular surgeries** and is a well-known risk factor for postoperative morbidity and mortality. Excessive blood loss frequently requires the transfusion of allogenic blood, blood products, and surgical re-exploration when appropriate. Re-exploration may not reveal a surgically repairable source of bleeding in up to 50% of cases. Both massive blood transfusion and re-exploration are associated with longer intensive care and hospital stay, wound infection, higher morbidity, and reduced survival rates. The high risk of bleeding and its consequences have prompted cardiac surgeons to explore the off-label use of recombinant factor VIIa as an alternative haemostatic agent for postoperative bleeding (Murphy 2007, Zangrillo 2009, Goksedef 2010, Chapman 2011).

Recombinant factor VIIa (rFVIIa; NovoSeven®, NovoNordisk, Copenhagen, Denmark) is a recombinant DNA preparation of activated blood coagulation factor VII. It is an engineered preparation of factor VIIa produced in cultured baby hamster kidney cells and is nearly identical to plasma-derived factor VIIa in structure and function. At the pharmacological level, it is to some degree different from the natural FVIIa (nFVIIa). Its pharmacologic action induces thrombin generation on locally activated platelets and contributes to the formation of a stabilized clot at the site of vessel injury. NovoSeven received market approval by the US Food and Drug Administration (FDA) in 1999 for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX respectively. In 2005, it was further approved by the FDA for the treatment of bleeding episodes and for the prevention of bleeding in surgical interventions or invasive procedures in patients with acquired hemophilia. NovoSeven is licensed in Europe for the treatment of congenital factor VII deficiency and Glanzmann's thrombasthenia refractory to platelet administration (Ratko 2004, Al-Ruzzeh 2008, Gill 2009, Zangrillo 2009, Logan 2011, Goksedef 2012, Guzette 2012).

Over the last decade, rFVIIa (NovoSeven) has been increasingly used off-label for a wide range of disorders including life threatening bleeding after body and brain trauma, intracranial hemorrhage, major abdominal surgeries, drug-induced coagulopathy, platelet disorders, intraoperative or postoperative hemorrhage, and a number of other conditions. The vast majority of adults and pediatric patients who have received rFVIIa received it for an off-label indication. It is also being used off-label for pediatric and adult cardiac surgery. However, its use in these patients is controversial and widely debated due to the concern about its safety especially for the potential increase the risk of thromboembolic events. Cardiac surgery patients are already at high risk of myocardial ischemia, arterial and venous thrombosis before, during, and after the surgery due to either or both the underlining pathology and the surgery performed with cardiopulmonary bypass or cross clamping. The reported mortality and complication rate among cardiac surgery patients receiving rFVIIa ranged from 19-40%. The issue of the appropriate dosing is also a major concern (Ratko 2004, Al-Ruzzeh 2008, Gelsomino 2008, Gill 2009, Zangrillo 2009, Logan 2011, Goksedef 2012, Guzette 2012).

 Back to Top

Medical Technology Assessment Committee (MTAC)

***NovoSeven*®**

10/10/2001: MTAC REVIEW

Evidence Conclusion: There is insufficient published scientific evidence on which to base conclusions about the effect of NovoSeven® on health outcomes in people with Glanzmann's disease.

Articles: The search yielded 7 articles. Two were review articles, two were case studies (report on only one patient) and three were case series, each of which included five or fewer patients with Glanzmann's disease. Due to the small sizes of the case series, no evidence tables created.

The use of NovoSeven® in the treatment of Glanzmann's disease does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

***NovoSeven*®**

12/10/2003: MTAC REVIEW

Evidence Conclusion: There are no studies comparing NovoSeven to another treatment for hemophilia patients with inhibitors. A comparison to the alternative bypass agents, prothrombin complex concentrates (PCCs) or activated prothombin complex concentrates (aPCC), might be feasible. In the Scharrer study, 7 (25%) of the patients had failed PCCs/aPCCs, but neither of the other two studies attempted to select patients who had failed treatment with another bypass agent. Non-comparative clinical data suggests that NovoSeven is effective at achieving hemostasis in 80-90% of bleeding episodes. There are data on both in-home and surgical use of NovoSeven. There was a low rate of thrombosis associated with treatment in the published data.

Articles: The search yielded 71 articles, many of which were reviews, opinion pieces, overviews or dealt with technical aspects of the treatment. There were no randomized or non-randomized studies with hemophilia patients with inhibitors that compared NovoSeven to an alternate treatment. One randomized controlled trial was identified with hemophilia patients, but this compared two doses of NovoSeven. The remaining empirical studies were case series. The RCT was critically appraised, not for comparative data, but because it was a reasonably well-designed study with the target population. In addition, two of the largest case series using NovoSeven to treat hemophilia patients with inhibitors were critically appraised. The articles reviewed are as follows: Shapiro AD, Gilchrist S, Hoots WK. Prospective, randomized trial of two doses of rFVIIa (NovoSeven) in hemophilia patients with inhibitors undergoing surgery. *Thromb Haemost* 1998; 80: 773-778. See Evidence Table. Key NS Aledort LM, Beardsley D. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (NovoSeven) in hemophiliacs with inhibitors. *Thromb Haemost* 1998; 80: 912-918. See Evidence Table. Scharrer I et al. Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor II deficiency. *Hemophilia* 1999; 5: 253-259. See Evidence Table.

The use of NovoSeven® in the treatment of Hemophilia does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

***NovoSeven*®**

02/11/2013: MTAC REVIEW

Evidence Conclusion: There is a lack of published high-quality studies on the off-label use of rFVIIa in cardiac surgery. To date only two RCTs evaluated the use of rFVIIa in adult cardiac surgery; one was a very small pilot study with 20 patients that assessed the prophylactic use of the therapy, and the other was conducted among 172 patients (Gill 2009, evidence table 3) to evaluate the effectiveness and safety of rFVIIa in 172 patients bleeding after cardiac surgery requiring cardiopulmonary bypass. Both trials lacked statistical power to detect significant differences between the study groups. The rest of the published studies were observational with or without matched comparison groups. A number of these observational studies compared outcomes of patients receiving rFVIIa to matched groups using propensity score (PS) analysis. This method is used to adjust for selection bias in observational studies of causal effect, when RCTs are unfeasible, unethical, or too costly to conduct. PS matching adjusts for observed variables and can only decrease but not eliminate the selection bias. It may also reduce the study's external validity as only a subset of the treated patients is used in the analysis. The majority of the published studies were conducted over a long period of time; the administration of rFVIIa was based on the guidelines of each institution, but was ultimately made by at the discretion of the operating team, and may have evolved throughout the study period as the experience with using the therapy increased (Anderson 2012). There were no consistent well-defined and measurable endpoints to evaluate the efficacy of the therapy. In addition, the published studies followed different protocols for the threshold for using rFVIIa and its dose. This ranged from prophylactic use as a haemostatic agent in the operating room, to a rescue therapy for

 Back to Top

patients with refractory bleeding. Rescue therapy is defined as situations in which rFVII is used when patients continue to bleed excessively despite having received maximal standard haemostatic therapy, the definition of which varied between institutions (Guzette 2012).The dosage of rFVIIa ranged between studies from 9-192 µg/kg, and was used either repeatedly or a in a single dose.The results of the RCTs and the four comparative observational studies on the use of rFVIIa in adult cardiac surgery were pooled in three meta-analyses (Zangrillo 2009, Ponschab 2011, and Yank 2011). The pooled results of the two more recent meta-analyses comprising a total 470 patients, showed no significant effect of rFVIIa on reducing mortality compared to usual care, but a statistically significant increase in the occurrence of stroke (calculated number needed to harm of 26). The meta-analyses showed a lower but statistically insignificant rate of re-exploration and a trend towards the lower blood loss and need for transfusion with the use of rFVIIa. Gill and colleagues' RCT found a statistically significant lower rate of re-operation rates and need for blood transfusion, and a statistically insignificant increase in serious adverse events in the adult cardiac surgery patients who received rFVIIa. In conclusion, the available evidence suggests that rFVIIa use in adult cardiac surgery patients may result in an increased risk of stroke and lower re-exploration rate without a significant mortality benefit. Larger randomized controlled trials with sufficient power are needed to verify the results of the meta-analyses and clearly assess the benefits and risks of the off-label use of rFVIIa in cardiac surgery patients.

Articles: The literature search for studies on the use of rFVIIa (NovoSeven) for adults undergoing cardiac surgery revealed two meta-analyses, two randomized controlled trials, and a number of observational prospective and retrospective studies with or without comparison groups. The search also identified an updated Cochrane review and other meta-analyses and systematic reviews that included trials on the use of rFVII for any off-label indication including cardiac surgery. Among these, there was one review (Yank 2011) prepared for the agency for Healthcare Research and Quality (AHRQ) that included a meta-analysis of studies on the use of the rFVIIa for adult cardiac surgery. The two meta-analyses on the use of rFVIIa or cardiac surgery patients were conducted by the same group of authors, but the more recent analysis included an additional RCT and focused on the rates of thromboembolic events associated with the use of rFVIIa. Two meta-analyses of trials using rFVII for adult patients undergoing cardiac surgery as well as the most recent RCT among cardiac surgery patients were selected for critical appraisal. Zangrillo A, Mizzi A, Biondi-Zoccai G, et al. Recombinant activated factor VII in cardiac surgery: a meta-analysis. J Cardiothoracic Vasc Anesth. 2009.23:34-40. Evidence Table. Ponschab M, Landoni G, Biondi-Zoccai G, etal. Recombinant activated factor VII increases stroke in cardiac surgery: a meta-analysis. J Cardiothoracic Vasc Anesth. 2011.25:804-810. Evidence Table.Gill Ravi, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor VII A randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. Circulation 2009; 120:21-27. Evidence Table.

The use of NovoSeven® in the prevention of cardiac surgery bleeding does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
J7189	Factor VIIa (antihemophilic factor, recombinant), (NovoSeven RT), 1 mcg

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

Date Created	Date Reviewed	Date Last Revised
10/10/2001	10/10/2001, 12/10/2003, Reinstitute criteria set on 03/05/2013[MDCRPC] 03/05/2013[MDCRPC], 01/07/2014[MDCRPC], 11/04/2014 [MPC], 09/01/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 01/08/2019[MPC], 01/07/2020[MPC], 01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC], 03/12/2024[MPC]	03/05/2013

Back to Top

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description

Back to Top