

# Recombinant Activated Factor VII for Prevention of Bleeding Unrelated to Hemophilia: Clinical and Economic Systematic Review

## Executive Summary

### The Issue

Recombinant activated factor VII (rFVIIa) is a hemostatic agent that is approved for the treatment of bleeding episodes in hemophilia A or B patients with clotting factor inhibitors. It is being used beyond the approved indications by non-hemophilia patients undergoing surgery. Recombinant FVIIa is costly, and it is unclear if the benefit of the off-label use of rFVIIa outweighs the potential harms and costs.

### Objectives

This report assesses the impact of using rFVIIa for the prevention of bleeding in patients without hemophilia or other inherited bleeding disorders.

The research questions are:

1. What is the clinical effectiveness of evaluated doses and regimens of rFVIIa compared with placebo, no treatment, or other standard therapies for the prevention of bleeding associated with liver transplantation, prostatectomy, cardiac surgery, or supra-therapeutic anticoagulation in individuals without hemophilia, inherited platelet disorders, or other coagulopathies?
2. What are the practice guidelines for monitoring safety and efficacy of rFVIIa when used for the prevention of bleeding associated with liver transplantation, prostatectomy, cardiac surgery, or supra-therapeutic anticoagulation in individuals without hemophilia, inherited platelet disorders, or other coagulopathies?
3. What is the cost-effectiveness of rFVIIa compared with placebo, no treatment, or other standard therapies when used for liver transplantation, prostatectomy, cardiac surgery, or supra-therapeutic anticoagulation in individuals without hemophilia, inherited platelet disorders, or other coagulopathies?

### Methods

A systematic review of the clinical and economic literature was conducted. Randomized controlled trials (RCTs), non-randomized controlled clinical trials, prospective controlled observational studies, evidence based guidelines, and economic analyses that met the inclusion criteria were included in the review. The selection of studies and extraction of data were completed independently by two researchers.

## Clinical Effectiveness

Eight RCTs and two cohort studies focused on surgical patients who received rFVIIa, placebo, or usual care for the prevention of bleeding. No studies evaluated rFVIIa for the prevention of bleeding in patients receiving anticoagulation agents. Two evidence-based guidelines stated that there is no specific method to monitor the efficacy of rFVIIa treatment for the prevention of bleeding.

Because of the heterogeneity among the small numbers of studies that were identified for each indication, a narrative synthesis was conducted. Most trials did not report the mean differences between groups or associated 95% confidence intervals. Instead, they summarized the comparisons between groups using descriptive statistics and P values resulting from hypothesis testing. When the estimates of between-group differences were unavailable, the interpretations of findings as presented by study authors were summarized.

In an RCT involving 82 pediatric cardiac surgery patients, no statistically significant difference was detected favouring rFVIIa therapy compared with placebo for the volume of red blood cells or platelets transfused, or operative time. In one RCT involving 20 adults undergoing cardiac surgery, no statistically significant difference was found between rFVIIa and placebo in any outcome that was measured (volume of blood products, length of stay, or adverse events). A second placebo-controlled RCT (22 patients) reported statistically significant reductions favouring rFVIIa in the volume of red blood cells or platelets transfused and in the length of intensive care unit stay.

In adult patients undergoing liver transplantation, two small RCTs (25 or fewer patients in each trial) reported that rFVIIa statistically significantly reduced the volume of red blood cells and fresh frozen plasma that was transfused compared with placebo or usual care. No statistically significant differences in the volume of blood products that was transfused were detected among patients who received rFVIIa during one placebo-controlled trial involving 87 patients and during another placebo-controlled trial involving 209 patients. The length of hospital or intensive care unit stay was similar between rFVIIa and control groups. One of four RCTs reported that the use of rFVIIa statistically significantly lowered the duration of the surgical transplantation procedure.

An RCT involving 36 patients undergoing prostatectomy concluded that the use of rFVIIa reduced the need for red blood cell transfusion and reduced the operative time compared with placebo. No statistically significant differences were detected between groups in the length of hospital stay, number of adverse events, or number of deaths.

It was not possible to adequately evaluate the risk of adverse events that was associated with the prophylactic use of rFVIIa during surgery. Adverse event data were poorly reported in the clinical trials, and the studies were not designed to detect differences in the incidence of uncommon events. Most studies excluded patients at risk of thromboembolic events. The strength of evidence was limited by the quality and quantity of the literature available. There was a low risk of bias in two of eight RCTs. In six studies, the risk of bias was unclear.

### **Economic Review**

Three studies reported the costs and consequences of treatment in three different indications. The findings of these studies were presented in a narrative synthesis. A retrospective study of liver transplantation found no difference in costs or outcomes between patients who were treated using rFVIIa and those receiving usual care. A randomized, placebo-controlled trial in cardiac valve replacement reported less use of blood products, shorter intensive care unit stays, and higher costs for patients who were randomized to receive therapy using rFVIIa. A randomized, placebo-controlled trial of abdominal prostatectomy reported a dose-response effect in the number of packed cell units transfused and a shorter operating time for patients receiving rFVIIa. There was no evaluation of outcomes beyond the hospital stay in the three studies. Total hospital costs were lower for patients receiving the higher dose of rFVIIa compared with placebo. All three studies had limitations in that data were obtained from one hospital centre, the studies on which they were based had small sample sizes, the assessments of outcomes and costs were limited to the duration of the inpatient stay, and the health states were not evaluated. The three studies were not reported in sufficient detail to permit a complete assessment of the methods and results, and generalizability to a Canadian setting was limited.

### **Health Services Impact**

There is little use of rFVIIa for the prevention of bleeding in Canada, because of concerns about thromboembolic adverse events relative to potential benefit. For this reason, a formal budget impact analysis was not conducted. If future clinical research finds rFVIIa to be efficacious and to be associated with a low risk of thromboembolic events, as many as 33,000 cardiac surgery, liver transplant surgery, and prostatectomy patients, combined, may be eligible for this treatment in Canada each year.

## Conclusions

No consistent benefit of rFVIIa therapy was detected among studies evaluating the prevention of bleeding in patients undergoing prostatectomy, liver transplantation, or cardiac surgery. The risk of adverse events after the prophylactic use of rFVIIa in surgical patients is unknown. No conclusions can be drawn on the effectiveness or safety of using rFVIIa in the prevention of bleeding in patients who have received supra-therapeutic doses of anticoagulant agents. When used for prevention of bleeding, no specific method is available to monitor the effectiveness of rFVIIa.

Given the small number of economic studies available and limitations in the reporting, methods, and generalizability of these studies, conclusions about the cost-effectiveness of using rFVIIa to prevent bleeding in a Canadian setting cannot be made. An informative primary economic evaluation might be more appropriate when consistent effectiveness evidence is available and preventive use of this treatment more commonplace. As a result, the cost-effectiveness of using rFVIIa in the prevention of bleeding unrelated to hemophilia remains unknown. If rFVIIa is used preventively on a wider scale by clinicians in the future, the potentially eligible population for this treatment is substantial.