# National Essential Medicines List
# Tertiary/Quaternary Medication Review Process

**Date:** September 2017

**Medication:** Haemophilia bypassing agents

- Recombinant Factor VIIa (rVIIa)
- Activated Prothrombin Complex Concentrate (aPCC)

**Indication:** Haemophilia with inhibitors (on demand, when presenting with a significant bleed)

**Introduction***:*
Haemophilia A and B is treated using FVIII-replacement or Factor FIX therapy, but administration of the factor can lead to the development of anti-FVIII or FIX antibodies, commonly known as inhibitors. These inhibitors interfere with the factor function and prevent coagulation. Inhibitors are usually IgG antibodies that neutralise the procoagulant activity of FVIII or FIX. About 10 - 15% of haemophilia A patients and 1 - 3% of haemophilia B patients may develop persistent inhibitors, which make treatment with factor concentrates difficult.[1]

**Contextualization**
For haemophiliacs with high titre inhibitors there is no other treatment options available to stop bleeding. Life threatening bleeds will be associated with significant mortality, or prolonged ICU stay if bleeding cannot be controlled. Non-life threatening bleeds such as joint bleeds will lead to debilitating haemophilic arthropathy, rendering these patients disabled, and not economically active. Furthermore, it is not possible to perform any surgical intervention (e.g. appendectomy) without bypassing agent cover.

**Evidence:**
There is no alternative for patients with high titre inhibitors [>5 *Bethesda units* (BU)]. Approximately 30% of patients with inhibitors preferentially respond to either rVIIa or aPCC. This inter individual variation is not clinically predictable, and require that both agents be available.
Low titre (<5 BU), low responding inhibitors (Not increasing >5 BU following Factor 8 challenge) could potentially be managed by high doses (2 to 3 times dose) of standard Factor VIII concentrate.

***Efficacy and safety***
**Recombinant Factor VIIa vs aPCC**
rFVIIa and aPCC have been shown to have similar efficacy and safety.[2,3]

**Recommendation:**
The Committee recommends that one bypassing agent be available on the EML, as a class. The alternative bypassing agent should also be available as emergency stock on a named patient basis for patients not responding to the EML item. The use of these agents should be under the guidance of clinicians skilled in the management of patients with haemophilia. Their use should be managed and monitored by local Pharmacy and Therapeutics Committees. Where possible all haemophilia patients should be treated in haemophilia comprehensive care centers.

**Review indicators**:
- availability of novel bypassing agents
- health economic considerations

[1] Mahlangu J, Gillham A. Treatment Guidelines for Haemophilia in South Africa. SAMJ 2008, 98(2):127-138.
[2] Astermark J, et.al. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. Blood 2007; 109: 546–51.
[3] Matino D, Makris M et. al. Recombinant factor VIIa concentrate versus plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors. Cochrane Database Syst Rev. 2015