



GUIDELINES FOR MANAGEMENT OF FACTOR VII DEFICIENCY

Australian Haemophilia Centre Directors'
Organisation

May 2010

Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case. The guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of compilation (May 2010).

These guidelines will be reviewed in 2013.

1. Introduction

Factor VII deficiency is a rare congenital bleeding disorder characterised by spontaneous bleeding episodes in severely affected individuals and bleeding following trauma or surgery in mildly affected individuals. In severely affected individuals there is a significant risk of cerebral haemorrhage in the first year of life [1]. The incidence is 1 per 500,000 and inheritance is autosomal recessive [2]. Severe haemorrhagic manifestations are associated with levels of factor VII < 1% and mild bleeding symptoms may be seen in those with Factor VII > 5%. The response to surgery is variable, with some patients tolerating well, although dental extraction is commonly associated with bleeding. While FVII deficiency may increase the risk of bleeding it does not necessarily protect against thrombosis [3]. Patients should be treated in Haemophilia Treatment Centres, with close laboratory monitoring.

The half life of factor VII is 3-6 hours [2] and a factor level of 10-15% is adequate for most surgical procedures [4].

2. Treatment Products Available in Australia

2.1. Recombinant factor VIIa

2.1.1. *NovoSeven (Novo Nordisk)*. Factor VII is produced as a single-chain glycoprotein (406 amino acids, 50 kDa), in a genetically transformed baby hamster kidney cell line. Purification is by ion exchange and immunoaffinity chromatography using murine monoclonal antibodies. During purification recombinant factor VII is converted to the two-chain activated form. The recombinant factor VIIa is formulated as a freeze dried preparation and contains noncoagulation factor contaminants as a result of the manufacturing process. These include trace amounts of hamster proteins from cells used in the fermentation process; bovine IgG and other bovine proteins from the bovine serum in the fermentation medium; and

mouse IgG from the anti- FVII monoclonal antibody used in purification.

2.2. Plasma derived factor VII concentrate

2.2.1. Factor VII (Baxter). This is a high purity concentrate. The manufacturing procedure includes a two step vapour heat inactivation at 60°C for 10 hours, followed by 80°C for 1 hour. Both steps are carried out under excess barometric pressure. The plasma procurement program provides for non-returning donor exclusion and a three month inventory hold on each plasma donation with look-back procedure. A PCR test for virus genome sequences of HIV, HBV and HCV is carried out on all batches.

2.2.2. Factor VII (BPL). This concentrate is manufactured in the UK from plasma sourced from FDA approved sites in the USA. It is a highly purified concentrate prepared using ion-exchange chromatography. The product is subjected to dry heat treatment at 80° for 72 hours.

3. Treatment Regimens

In principle the use of a recombinant product, if available, is favoured over a plasma derived concentrate. Recombinant factor VIIa is registered with the TGA for this indication. Plasma derived factor VII is available through the TGA's Special Access Scheme

3.1. Recombinant factor VIIa [5]

Haemarthrosis - 20-25 µg/kg as single dose

Traumatic haemorrhage – depending on severity up to 20-25 µg/kg repeated every 2-3 hours.

Surgery – 20-25 µg/ kg repeated every 2-3 hours for the first 24 hours, extending intervals from 3 to 8 hours until healing is complete.

3.2. Plasma derived factor VII concentrate

Haemarthrosis- 10 IU/kg

Surgery- 8-40 IU/kg every 4-6 hours for up to 10 days

Alternatively 30-40 IU/kg twice per day [4]

3.3. Concomitant use of tranexamic acid

The concomitant use of tranexamic acid, at a dose of 60-100 mg/kg/day, given orally or intravenously in divided doses three to four times a day, should be considered.

3.4. Prophylaxis in severely deficient patients

Prophylaxis may be considered with one of the available products and the clinical response closely monitored.

4. Thrombotic Risk

There are rare reports of thrombosis in patients with factor VII deficiency (even those with severe deficiency). These thrombotic events have occurred mostly in association with known thrombotic risk factors such as surgery or periods of factor replacement. However, there are also reports of spontaneous or idiopathic thrombosis. The risk of thrombosis should be taken into account in evaluating the need and the dose of replacement therapy, when surgical intervention is planned [6]. Consideration should also be given to the use of routine thromboprophylaxis

REFERENCES

1. Triplett D, Brandt J, McGann Batard M, Schaeffer Dixon J, Fair D. Hereditary factor VII deficiency: Heterogeneity defined by combined functional and immunochemical analysis. *Blood*, 1985,66:1284-1287.
2. Bauer KA. Treatment of factor VII Deficiency with Recombinant Factor VIIa. *Haemostasis*, 1996, 26(supp 1):155-158.

3. Marty S. et al. The paradoxical association between inherited factor VII deficiency and venous thrombosis. *Haemophilia* 2008 May;14(3):564-70).
4. Peyvandi F, Manucci PM. Rare Coagulation Disorders. *Thromb Haemost* 1999; 82: 1207-14
5. Mariani G. et al. Use of recombinant, activated factor VII in the treatment of congenital factor VII deficiencies. *Vox Sanguinis* 1999;77;131-136
6. Mariani G. Et al. Thrombosis in inherited factor VII deficiency. *J Thromb Haemost.* 2003 Oct;1(10):2153-8