

# Initiation of Prophylaxis with Clotting Factor Concentrate and Home Therapy - Full Clinical Guideline

Reference no.: CG-HAEM/2024/007

## 1. Introduction

Coagulation factor replacement in patients with haemophilia A or B may be given in response to a bleed (on-demand therapy) or given regularly to prevent such bleeds (prophylactic therapy).

The goal of prophylactic treatment is to prevent bleeding, primarily into the joints, with subsequent development of arthropathy. Importantly, prophylactic treatment will also offer protection from other serious bleeds such as intracranial bleeds, muscle bleeds and intra-abdominal bleeds. Prophylaxis may be given as primary or secondary, or as episodic.

High level evidence-based studies of prophylaxis in boys with haemophilia A have been published and there is now a widespread recognition of the efficacy of the early implementation of prophylaxis in the prevention of arthropathy in children and young adults (Manco-Johnson et al, 2007; Gringeri et al, 2009). There is less evidence for prophylaxis in haemophilia B, but consensus among haemophilia treaters is that children with severe haemophilia B should be treated similarly (with important considerations for initiation of prophylaxis – see Page 4).

Primary prophylaxis is started prior to initiation of joint disease usually well before the age of 2 or after the first joint bleed. The rationale behind an early start is that even a small number of joint bleeds can result in irreversible damage, and that damage may progress despite prophylactic therapy. It has also been shown that the time point at which prophylaxis is begun is an independent factor for good joint outcome.

## 2. Aim and Purpose

To enable and ensure that prophylaxis with clotting factor concentrate in Children with Haemophilia is started at the right time and monitored appropriately with the aim of preventing joint and muscle disease.

## 3. Definitions, Keywords

Haemophilia A - Congenital deficiency of clotting factor VIII; Haemophilia B - Congenital deficiency of clotting factor IX. Severe haemophilia is associated with spontaneous bleeding into joints, muscles and organs e.g. the brain.

## 4. Main body of Guidelines

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### **Choice of factor concentrate**

Current practice in the UK is to treat all previously untreated patients (PUPs) with a recombinant factor concentrate. Recent evidence from the SIPPET study comparing inhibitor rates between PUPs treated with recombinant vs plasma derived concentrates may be discussed with parents/carers depending on the clinical context.

A decision should be made regarding the product to be used in advance of the child requiring any treatment with recombinant factor VIII. This should be discussed with the child's parents and documented in the notes and the electronic record.

### **Initiation of prophylaxis**

#### **Escalation to CCC:**

**All newly diagnosed severe haemophiliacs and initiation of prophylaxis must be discussed with the CCC**

Prophylaxis should be commenced at the latest after the 1<sup>st</sup> joint bleed or significant soft tissue bleed.

The decision of when to start prophylaxis for a child over the age of one who has not experienced any bleeds should be made on an individual basis.

Indications to start prophylaxis prior to the second joint bleed/significant soft tissue bleed include:

- Following treatment for an intracranial haemorrhage
- Following an early intensive treatment episode, e.g. treatment to cover a surgical procedure
- If a child is requiring frequent on-demand treatment for injuries such as minor soft tissue injuries and minor head injuries

### ***Severe haemophilia A***

In most circumstances prophylaxis should be commenced at a dose of 25-50 iu/kg factor VIII (round up to the nearest whole vial size) once weekly. Factor concentrate will be administered via a peripheral vein where possible. A central venous access device (CVAD) may be required where venous access is difficult or to facilitate home treatment. The dose should be escalated in 2-3 steps aiming for a final prophylactic regimen of 25-50 iu/kg every 48 hours. If circumstances dictate otherwise, such as the child needing to attend the haemophilia unit for prophylaxis, a 3 times per week regimen can be used. If venous access allows, treatment should be escalated rapidly in order to prevent haemarthroses or soft tissue bleeds.

If prophylaxis is commenced following treatment of an intracranial haemorrhage or an intensive treatment episode, it should be initiated at a dose of 50 iu/kg (round up to the nearest whole vial size) administered at least every 48 hours (dosing should be guided by trough levels and/or PK measurement – see Page 5).

### ***Severe haemophilia B***

There is a lack of evidence to guide the initiation of prophylaxis in children with severe haemophilia B.

It is reasonable to initiate prophylaxis with recombinant factor IX 50 iu/kg once weekly for most patients (an exception would be if prophylaxis was commenced after treatment of an intracranial haemorrhage) and escalate to twice weekly administration of factor concentrate at a dose of 25-50 iu/kg.

As for children with severe haemophilia A, the prophylaxis dose should be rounded up to the nearest whole vial size and the insertion of a CVAD should be considered if venous access/adherence to treatment is difficult.

**NOTE: Factor IX inhibitors are associated with allergic/anaphylactic reactions to recombinant factor IX. The 1<sup>st</sup> 20 doses of recombinant factor IX should be given in a clinical area where paediatric resuscitation facilities are available, i.e. E39 day care or the Childrens' ED. If any allergic reaction occurs, an inhibitor should be excluded prior to further factor IX exposure.**

## Monitoring of children on prophylaxis

### **Monitoring for inhibitors**

Please see the inhibitor guideline: [Surveillance and management of inhibitors in congenital haemophilia - Full Clinical Guideline](#) for information on inhibitor surveillance.

### **Monitoring for efficacy**

A combination of clinical and laboratory monitoring is required for children on prophylaxis.

- All parents/carers/children on prophylaxis will record their treatment using the online system Haemtrack. This will record all prophylactic treatment and also document bleeding episodes and response to treatment. Haemtrack records will be reviewed at each routine clinic visit. If bleeds are occurring, the haemophilia team will be alerted by the online system allowing the opportunity to review treatment outside of usual clinic visits.
- All patients with severe haemophilia should have their own personalised treatment plan documenting their current prophylactic regime as well as dose recommendations for any breakthrough bleeding episodes. A copy of this plan will be available in the patient's hospital record and given to the patient/parent/carer. The plan should be updated at each routine clinic visit. (example appendix 1)
- All patients receiving prophylaxis over the age of 4 years will have a Haemophilia Joint Health Score recorded at least once a year. Younger children should have a clinical assessment by an experienced haemophilia physiotherapist recorded at each routine clinic visit.
- Trough factor levels should be measured at routine clinic visits (at least 6 monthly). A target of trough factor level > 1% has historically been used. This may not be sufficient to prevent bleeding in all patients depending on phenotype and level of physical activity. In addition, some patients with trough levels <1% may not experience breakthrough bleeds. Prophylaxis should be personalised to each individual depending on various factors such as activity levels, bleeding phenotype, venous access etc. The use of population PK modelling where available (currently only MyPKFit for patients on Advate) is increasingly being used to tailor prophylaxis and should be used when possible.
- Prophylaxis should be tailored to provide maximum protection for physical activity and schooling. In most cases treatment should be administered in the morning to optimise factor levels for maximum benefit.

## Home treatment

Adherence to a prescribed regimen of prophylaxis is essential to ensure the full benefits of prophylaxis are realised. Much of the burden of prophylaxis administration in children is unseen as it is undertaken by parents and then by the child when he is able to be taught self-administration. This is a significant commitment for any lay person. Successful prophylaxis involves several key components:

- Competent venous access techniques
- Ensuring an available supply of clotting factor concentrate and other disposable equipment
- Knowledge of appropriate storage and safe disposal of used items
- Detailed data collection
- Sensitivity to deal with psychological and emotional distress in the child
- Knowledge of symptoms of specific spontaneous and traumatic bleeds and their necessary treatment
- Knowledge of how and when to seek professional advice from haemophilia specialists.

All children will be offered home treatment and parents/carers will be provided with appropriate training delivered by a haemophilia nurse specialist/Kiteteam in order to achieve this.

All patients on prophylaxis will be offered home delivery of their factor concentrate once compliance with the online Haemtrack system has been demonstrated.

Parents/carers and later patients will be provided with appropriate education of how to recognise and treat bleeding episodes. Information will be provided (verbal and written) of how to contact the centre 24 hours a day for advice. Each patient will have a copy of their own personalised treatment plan (see Appendix 1 for example) for easy reference.

Relevant support for emotional or psychological difficulties associated with prophylaxis will be offered to the child and their parents/carers eg play specialists, clinical psychology.

An experienced physiotherapist is available to advise on appropriate physical activities for children of all ages. The importance of avoidance of head injury from contact sports and activities will be emphasised in an ongoing and age appropriate fashion.

## Appendix

**PROPHYLAXIS HOME TREATMENT REGIME**

Date: ..... Name: .....

Date of Birth: ..... NHS Number : .....

Diagnosis: ..... Factor Baseline: .....

Weight: ..... Factor Product: .....

**PROPHYLAXIS REGIME**

<b>Factor:</b>			
<b>Dose:</b>			
<b>Frequency:</b>			
<b>Comment:</b>			
<b>Desired Trough Level:</b>			
<b>Actual Trough Level:</b>		<b>Date:</b>	

**GUIDANCE TO MANAGEMENT OF A BLEED**

TYPE OF BLEED	TARGET FACTOR LEVEL	DOSE
Superficial bleed, nose or gum bleed, early joint/muscle bleed:	50 – 60%	
Moderate joint or deep muscle bleed:	60 – 80%	
Major joint bleed, stomach/bowel/head or airway bleed:	100%	

**! NOTE:** Dose is calculated according to your factor baseline level and your **weight**, it may therefore need to be adjusted from time to time. In many circumstances a follow up dose of factor is required. Round up to the nearest vial size.

If you have any questions or are in any doubt about treating your bleed, please contact the Haemophilia Team.

Name:.. .. Signature: ..... Date:.... ..

## References (including any links to NICE Guidance etc.)

1. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson, ML, Funk S, Jacobson L, Valentino LA, Hoots WK, Buchanan GR, DiMichele D, Recht M, Brown D, Leissing C, Bleak S, Cohen A, Mathew P, Matsunaga A, Medeiros D, Nugent D, Thomas GA, Thompson AA, McRedmond K, Soucie JM, Austin H & Evatt BL. (2007) Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *New England Journal of Medicine*, 357, 535–544.
2. Gringeri A, Lundin B, von Mackensen S, Mantovani LG & Mannucci PM. (2009) Primary and secondary prophylaxis in children with haemophilia A reduces bleeding frequency and arthropathy development compared to on-demand treatment: a 10-year, randomized, clinical trial. *Journal of Thrombosis and Haemostasis*, 7(Suppl. 2), 114–115 (Abstract OC-MO-034).
3. Richards M, Williams M, Chalmers E, Liesner R, Collins P, Vidler V, Hanley J. (2010) A United Kingdom Haemophilia Doctors' Organization Guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. *British Journal of Haematology*, 149, 498-507.
4. Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. (1992) Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med*, 232, 25–32.
5. Fischer K, Van De Bom JG, Molho P *et al.* (2002) Prophylactic versus on-demand treatment strategies was in for severe haemophilia: a comparison of costs and long-term outcome. *Haemophilia*, 8, 745–52.
6. Collins P, Chalmers E, Hart D, Liesner R, Rangarajan S, Talks K, Williams M, Hay C. (2013) Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia. *British Journal of Haematology*, 160, 153-170.

## 5. Documentation Controls

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