# Enhanced Half-Life Coagulation Factor Concentrates - Full Clinical Guideline

Reference no.: CG-HAEM/2024/009

## 1. Introduction

Three molecular strategies have been utilized to prolong the in vivo survival of FVIII and FIX coagulation factor concentrates (CFC). In these engineered CFCs, the native clotting factor glycoproteins have been modified via (i) addition of polyethylene glycol (PEG); (ii) fusion to recombinant human albumin; or (iii) fusion to the Fc-region of human IgG. These products have recently been commissioned to treat haemophilia A and B.

## 2. Aim and Purpose

To enable the safe and effective introduction of enhanced half life coagulation factor concentrates (EHL-CFC).

## 3. Definitions, Keywords

Enhanced half life coagulation factor concentrates (EHL-CFC).

Exposure Days (ED): number of days CFC is given to a patient.

ABR: annualised bleed rate.

Inhibitor: an antibody against factor VIII or IX which reduces the efficacy of CFC treatment.

## 4. Main body of Guidelines

In adults and adolescents (≥12 years), EHL-FVIII products have an average increase in half-life of about 1.5 times compared to the standard FVIII concentrates. EHL-FIX products have a 3–5 fold increase in half-life compared to standard FIX concentrates. These are average prolongations and there is wide inter-patient variability. As a consequence, the range of half-life with EHL-FVIII/IXs is larger than with the standard half-life products and it will not be appropriate to prescribe based on average half-life data for many patients.

All published data on EHLCFCs have excluded patients with a history of an inhibitor and it is possible that some of these patients will have shorter half-lives than those reported in clinical studies.

Published data for children (0–6 and 6–11 years) are limited, but the half-lives of EHL-FVIII/FIXs reported to date are shorter than in adolescents and adults (≥12 years). There is a progressive increase in half-life and incremental recovery (IR) across age bands and variability within each age band.The change in half-life and IR with age must be taken into account when prescribing EHL-CFCs to children.

In minimally treated severely affected patients, switching to an EHL-CFC can be considered after 50 EDs. In moderate/mild patients switching could be considered after fewer EDs. A limited half-life study should be performed. Minimally treated patients should be tested for an inhibitor before and at approximately 10 EDs after switching product.

**Switching to enhanced half-life coagulation factor concentrates.**

If a switch to an EHL-CFC is being considered, an initial consultation should be held to discuss opportunities, expectations and possible adverse reactions. Some individuals may have no increase in half-life when switching to an EHL-FVIII, while other patients will have an above average increase. It is important that patients are aware of these variations and that EHLFVIII may not allow a reduction in infusion frequency in all cases. The individual's bleed pattern and planned activity should be reviewed. The balance between activity, frequency of infusions and cost of treatment should be discussed. Discussions will differ markedly for EHLFVIIIs and EHL-FIXs and continuing with standard half-life CFCs may represent the best option for some individuals. The importance of establishing individualized pharmacokinetic data should be explained. The value of maintaining an accurate record of infusions and bleeds, for example, using Haemtrack, after a change in treatment regimen should be emphasised.

**Switching to an EHL-CFC**

When switching to an EHL-CFC, pharmacokinetic data should be obtained so that the individual's response to the agent is known.

Give a test dose of EHL-CFC (50u/ kg - children, 25–30u/ kg- adults). Measure levels as follows:

EHL-FVIII: preinfusion, 15 min post dose and approximately 6, 24, 48 and 72 h postinfusion.

EHL-FIX: preinfusion, 15 min postinfusion and approximately 24, 72, 120 and 168 h postinfusion.

After switching to an EHL-CFC, individuals should be followed up 4 weekly, in person or by other medium, for 3 months to assess the pattern of bleeds. Trough levels should be measured. An inhibitor screen should be performed at about 10 EDs and 3 months after switching or if clinically indicated.

All patients should be assessed for regimen efficacy based on annualised bleed rate, adherence, convenience, joint score and annualised treatment cost after 1 year on an EHL-CFC.

Treatment of bleeding episodes in patients on EHL-CFCs should be based on the severity of the bleed, the individual's incremental recovery, half-life and age. The first infusion should raise the FVIII/IX to a level appropriate for the type of bleed, taking into account the time and dose of the previous infusion. If bleeds do not resolve with two infusions, patients should

discuss further treatment with their Haemophilia Centre. Clinical review, measurement of FVIII/IX levels and inhibitor testing may be required to optimise management.

Prophylaxis with EHL-CFCs

Prophylactic regimens with EHL-CFCs should be tailored based upon individual pharmacokinetics and personal circumstances. Accurate records of infusions and bleeds are important for optimising treatment.

In some patients continuing with standard halflife products may be the preferred option. Typical initial regimens with EHL-CFCs in adults will be every 3rd or 4th day or twice a week depending on individual half-life in haemophilia A and once weekly in haemophilia B.

In a subgroup of adult patients, prophylaxis modification after switching may be possible based on bleed pattern such that treatment frequency can be further reduced to every 5 days or once weekly for haemophilia A and every 10– 14 days for haemophilia B. These are less costeffective regimens because a high total dose is required to maintain a target trough level.

The target ABR in children is zero. Due to shorter half-lives in this age group, it is unlikely that regimens less frequent than every 3rd or 4th day for haemophilia A and once weekly for haemophilia B will provide adequate prophylaxis. In addition, more frequent infusions may be required, especially for children.

**Surgery with EHL-CFCs**

An initial bolus infusion should be given to raise FVIII/IX to the predetermined level based on the known IR for the patient. Pre and post FVIII/IX levels should be measured to ensure that an adequate peak level is achieved.

• For major surgery, a fall off level should be measured postoperatively and on the following day to determine the time and dose of the next infusion based on clinical response and the minimum acceptable level.

• For haemophilia A, a second infusion on the day of surgery may be required. Infusions at least daily are likely to be required initially to maintain an adequate trough level following major surgery.

• For haemophilia B, once-daily dosing is likely to be feasible from day 1 and less frequently infusions may be possible if measured FIX levels are adequate.

**Monitoring enhanced half-life coagulation factor concentrates**

Laboratories should use an assay that has been validated for use with the specific EHL-CFC. This may be a chromogenic assay, a one stage assay with a method shown to give appropriate results or a one stage assay with an appropriate product specific standard.

Laboratories should not use an assay known to give discrepant values and multiply the result by a correction factor.

**Pharmacovigilance for enhanced half-life coagulation factor concentrates**

Information on adverse events should be reported to NHD (in the UK), the manufacturer and if appropriate EUHASS. For EHL-CFCs, this should include inhibitor formation, infection, death, allergy, malignancy, thrombosis and poor efficacy. Additional information that should be reported includes: off-label prescribing, prescribing errors and difficulties with monitoring. For PEGylated products, evidence of deterioration in renal function or neurological problems should be reported.

## 5. References

The use of enhanced half-life coagulation factor concentrates in routine clinical practice: guidance from UKHCDO. Haemophilia (2016), 22, 487–498.

## 6. Documentation Controls

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| Development of Guideline: | Angela McKernan |
| Consultation with: | Charlotte Grimley - Nottingham CCC |
| Approved By: | Thrombosis Group 5/3/19<br>Reviewed with no change - Dr McKernan -Dec 2023<br>CDCS Division - Jan 2024 |
| Review Date: | January 2027 |
| Key Contact: | Angela McKernan |