

Procurement of longer acting factor concentrates

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European Haemophilia Consortium Round Table of Stakeholders

Tenders and Procurement of Coagulation Factor Concentrates:

A European Survey of 38 countries

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Drug procurement

- Procurement of drugs is based **on selected drugs** and **dosage forms** and **available financial resources**.
- Procedures adopted in procuring drugs include:
 - Estimating quantity of each drug product required for a given period,
 - Finding out the prices of the different drug forms required
- Allocating funds for each drug depending on:
 - **Priority nature of the drug and its benefit**
 - Available finances

Standard products vs Longer acting products

Improvements with the longer-acting

	FVIII	FIX
<ul style="list-style-type: none">• Prolongation of the half-life<ul style="list-style-type: none">– (8-12 hours for FVIII concentrates and 18-24 hours for FIX concentrates)	Partial	0
<ul style="list-style-type: none">• Reduction of the number of injections	Partial	0
<ul style="list-style-type: none">• Less immunogenicity	Not available data yet	Not available data yet

Peculiarity of FVIII and FIX Longer acting Products

Product	Half-life extension technology	Mean $t_{1/2}$ (h) [minimum - maximum]	Half-life
FVIII products			
PEGylated			
BAY94-9027	Site-directed PEGylation	18,4 (13,7 - 28,1)	1,5 - 1,6 fold
N8-GP	Site-directed glycoPEGylation	19 (11,6 - 27,3)	
BAX855	N-glycosilation	18	
Fc-fusion			
rFVIII Fc (Eloctate)	Fc-fusion	18.8 (14.3-24.5)	1,5 fold
FIX products			
PEGylated			
N9-GP	Site-directed glycoPEGylation	93 (85-111)	6 fold
Fc- & Albumin fusion			
rFIX Fc (Alprolix)	Fc-fusion	82,1 (71,4 - 94,5)	3 - 4,6 fold
rIX-FP (CSL654)	Albumin-fusion	91,57	5 fold

1,5 – 1,6

3 – 6

What will be the benefits of longer acting FVIII & FIX?

1. Acute bleeding
2. Surgery
3. Prophylaxis

Acute events with standard vs longer acting products

	FVIII		FIX	
	Dosage (IU/kg)	Frequency	Dosage (IU/kg)	Frequency
Standard product				
Minor/Moderate	20-30°	every <u>12 to 24 hours</u>	20-50^	every <u>12 to 24 hours</u>
Major (Life threatening hemorrhages)	40-50°	every <u>8 to 24 hours</u>	50-100^	every <u>12 to 24 hours (~7 - 10 days)</u>
Long acting product				
Minor/Moderate	20-30 [§]	every <u>24 to 48 hours</u>	30-60 ⁺	every <u>48 hours</u>
Major (Life threatening hemorrhages)	40-60 [§]	every <u>12 to 24 hours</u>	80-100 ⁺	repeat infusions after <u>6-10 hours, then every 24 hours for the first 3 days, then every 48 hours</u>

(°Highlights of prescribing information to use Advate)

(§Highlights of prescribing information to use Eloctate, rFVIII-Fc)

(^Highlights of prescribing information to use BeneFIX)

(+Highlights of prescribing information to use Alprolix, rFIX-Fc)

Surgery with standard vs longer acting products

	FVIII			FIX		
	Dosage (IU/kg)	Frequency	Duration of therapy	Dosage (IU/kg)	Frequency	Duration of therapy
Standard product						
Minor	30-50°	every <u>12 to 24 hours</u>	1 - 3	20-50 [^]	every <u>12 to 24 hours</u>	1 - 2
Major						
Pre-operative	40-60°	//	//	50-100 [^]	every <u>12 to 24 hours</u>	
Post-operative	40-60°	every <u>8 to 24 hours</u>	1-7 days	40-60 [^]	every <u>12 hours</u>	7 - 10 days
Long acting product						
Minor/	25-40 [§]	every <u>24 hours</u>	At least 1 day	50-80 ⁺	every <u>48 hours</u>	A <u>single infusion</u> may be sufficient. Repeat as needed after 24-48 hours
Major						
Pre-operative	40-60 [§]	//	//			
Post-operative	40-50 [§]	every <u>8 to 24 hours and then every 24 hours</u>	At least 7 days	60-100 ⁺	Consider a repeat dose after 6-10 hours and then every 24 hours for the first 3 days.	

(°Highlights of prescribing information to use Advate)

(§Highlights of prescribing information to use Eloctate, rFVIII-Fc)

([^]Highlights of prescribing information to use BeneFIX)

(⁺Highlights of prescribing information to use Alprolix, rFIX-Fc)

Acute events and surgery

- Considerations -

- The doses of products used for an acute event are almost similar, particularly for FVIII (during the first 24-48 hours)
- The interval of infusions is extended particularly for FIX (after 24 hours), however more data are needed
- Therefore, the frequency of infusions might be reduced for FIX after 24 hours

How will change paradigm of prophylaxis with longer acting?

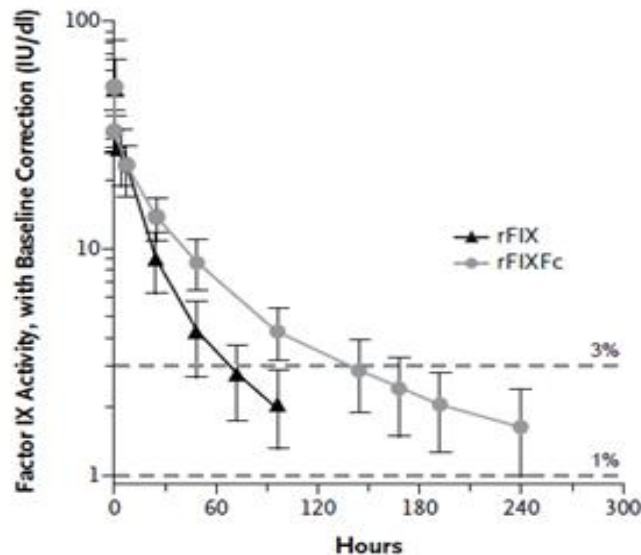
- Possible strategies are:
 - reduce the frequency of infusions and aim for a similar trough level
 - maintain the same frequency of infusions and achieve a higher trough

Pharmacokinetic parameters for rFIX-Fc

Product	Mean $t_{1/2}$ (h)	Time to 3 IU/dl (days)	Time to 1IU/dl (days)
Fc-fusion Products			
rFIX (BeneFIX)	*33,8 ^17,04	2,8	5,1
rFIXFc (Alprolix)	82,1 (3 - 4,6 fold)	5,8	11,2

(*based on a 96-hour sampling schedule)
(^based on a 48-hour sampling schedule)

(Following injection of 50 IU/kg)



- **Time to 1 IU/dL (1%) and 3 IU/dL (3%)** FIX trough level above baseline was **longer** for rFIX-Fc than for standard rFIX (11.2 days (95% CI, 10.2 to 12.4) and 5.8 days (95% CI, 5.1 to 6.6), respectively, for rFIXFc versus 5.1 days (95% CI, 4.6 to 5.7) and 2.8 days (95% CI, 2.6 to 3.1), respectively, for rFIX (P<0.001).

(Powell et al. N Engl J Med 2013;369:2313-23)

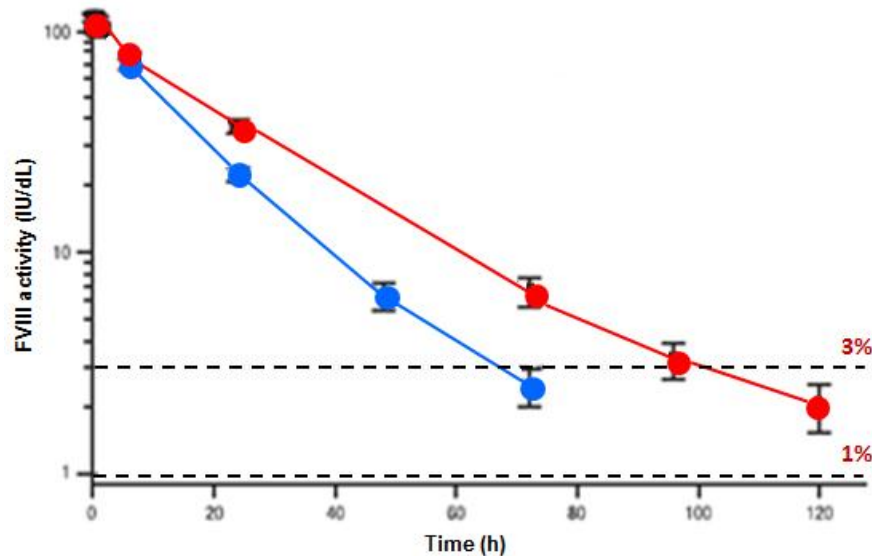
Decreased number of infusions

- Clinical data from studies with **FIX** longer acting suggest that once weekly or less infusions will be feasible:
 - **FIX Longer acting** → one infusion/week → **52 infusions/years**
 - Standard products → two infusions/week → **104 infusions/years**
- } Reduction of **50%**

FVIII activity vs time profile

Product	Mean $t_{1/2}$ (h)	Time to 3 IU/dl (days)	Time to 1 IU/dl (days)
Fc-fusion Products			
rFVIII (Advate)	12,4	2,5	3,3
rFVIII Fc (Eloctate)	18,8 (1,5 fold)	3,7	4,9

(Following injection of 50 IU/kg)



- **Time to 1 IU/dL (1%) and 3 IU/dL (3%)** above baseline (95% CI) FVIII trough level above baseline was **longer** for rFVIII Fc than for rFVIII, 4.9 (4.4-5.5) and 3.7 (3.3-4.1) days for rFVIII Fc vs 3.3 (3.0-3.7) and 2.5 (2.2-2.7) days for rFVIII, respectively (P < .001).

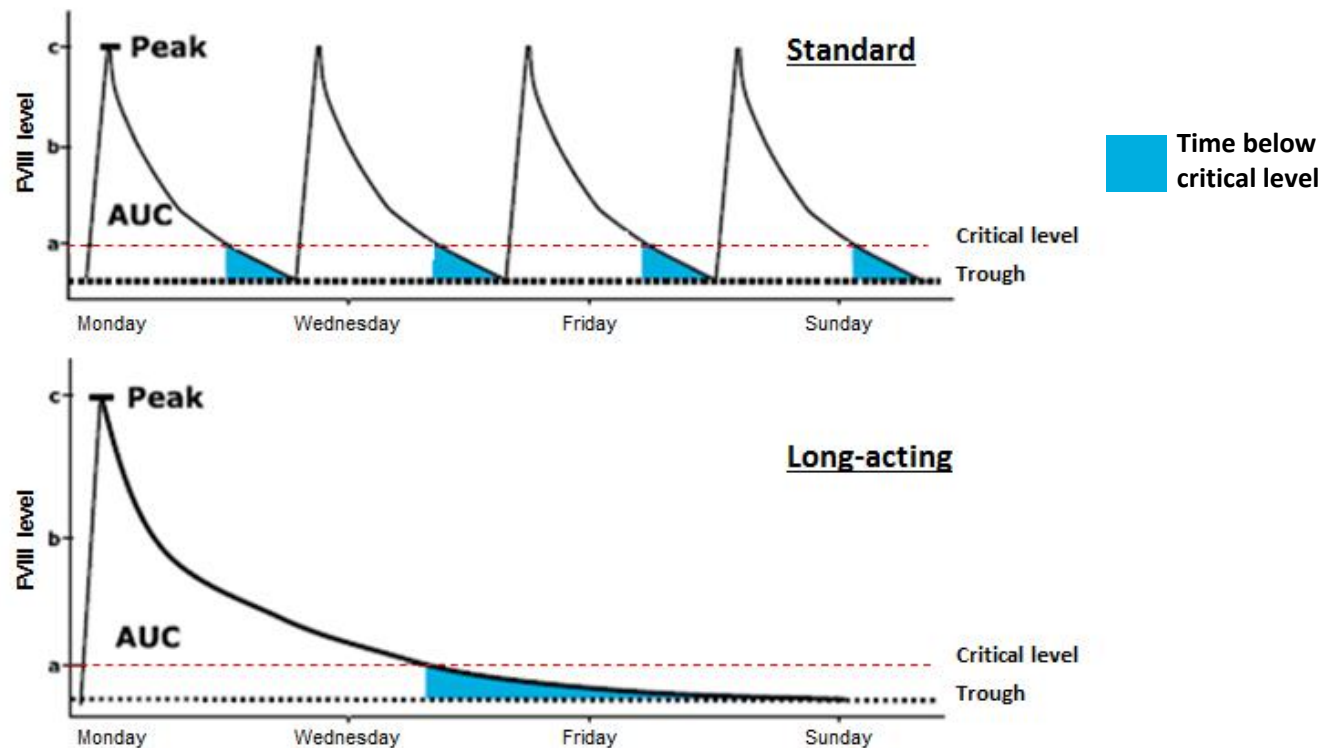
(Mahlangu et al. Blood 2014;123:317-325)

Decreased number of infusions

- Clinical data from studies with **FVIII** longer acting are less encouraging:
 - **FVIII Longer acting** → two infusions/week → **104 infusions/years**
 - Standard products → three infusions/week → **156 infusions/years**
- Reduction of **30 - 35%**

Impact on reduction of infusions

- Longer acting product infused once weekly present a longer time spent below the normal critical level
- Time with factor level $\leq 1\%$ is associated with breakthrough bleeding



Maximizing the interval between infusions will result in patients having **low factor levels for extended periods** of time during which they may be **at risk of bleeding.**

Product	Dose (IU/kg)	Treatment regimen	Median ABR, bleeds·patient ⁻¹ ·year ⁻¹	Patients with no bleeding episodes, %
Long-acting rFVIII Products				
BAY94-9027	45–60 IU/kg	every 5 days	1,9	44
	60 IU/kg	every 7 days	3,9	37
Eloctate (rFVIII-Fc)	25–65 IU/kg	every 3 - 5 days	1,6	45,3
	65 IU/kg	every 7 days	3,6	17,4
Long-acting rFIX Products				
Alprolix (rFIX-Fc)	50 IU/kg	every 7 days	3	23
	100 IU/kg	every 10 days	1,4	42,3

Patients treated with **rFVIII** longer acting on weekly prophylaxis experienced **a high ABR** in comparison to prophylaxis regimen every 3-5 days and this treatment regimen **did not provide adequate prophylaxis**

(Powell J et al. Haemophilia 2014;20;(Suppl.3):187

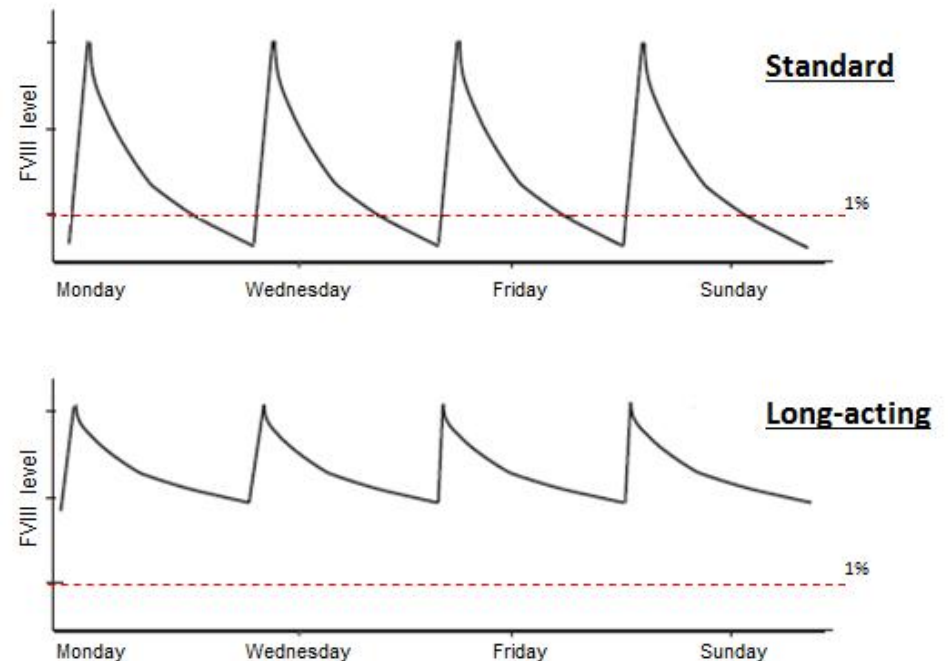
(Mahlangu et al. Blood 2014;123:317-325)

(Powell et al. N Engl J Med 2013;369:2313-23)

Higher trough levels?

An alternative strategy is to infuse **more frequently** to maintain a **higher trough level** with more frequent peaks.

- An individual taking standard FVIII every other day might choose to take a longer acting FVIII at the same frequency to maintain a higher trough
- The higher the trough level targeted, the less risk of bleeding
- Benefit of such therapeutic strategy needs to be evaluated in future



(Mahdi et al. Br J Haematol. 2015 ;169:768-76)

Changes in prophylaxis regimen

With longer acting products allowing:

- to infuse much less frequently → hemophilia B patients
- to maintain a higher trough level → hemophilia A and B patients

What will be the cost of this therapeutical strategies?

		Dose	Frequency	Number of infusions/year	IU/kg/year	cost/IU	cost/IU/kg/year
FVIII	Standard product						
		40 IU/Kg	3 times a week	156	6 248 IU/kg/y	X	X
	Long acting						
		65 IU/Kg	2 times a week	104	6 760 IU/kg/y	1,4 fold X	1,5 fold X
FIX	Standard product						
		40 IU/Kg	2 times a week	104	4 160 IU/kg/y	Y	Y
	Long acting						
		50 IU/Kg	1 times a week	52	2 600 IU/kg/y	2,3 fold Y	1,5 fold Y

Future prophylaxis regimens using **longer acting** factor concentrates are **not** likely to be **less expensive**.

		Dose	Frequency	Number of infusions/year	IU/kg/year	cost/IU	cost/IU/kg/year
FVIII	Standard product						
		40 IU/Kg	3 times a week	156	6 248 IU/kg/y	X	X
	Long acting			=	=		
		40 IU/Kg	3 times a week	156	6 248 IU/kg/y	1,4 fold X	1,3 fold X



Drug procurement

- **Finding out the prices** of the different drug dosage forms required
 - In Europe exist different tender and procurement systems:
 - tender process,
 - alternative procurement process
 - combination of a tender and alternative procurement process
 - Selection criteria include:
 - **Safety**
 - **Efficacy**
 - **Price**
 - Quality
 - Security of supply
 - The involvement of clinicians and patient organizations improves the outcome of procurement process

**The increase of cost of longer acting products
would be only justified by added benefits**