MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
4th November 2019

Agenda Item No	3.2
National Programme	Blood & Infection
Clinical Reference Group	Specialised Blood Disorders
URN	1716

Title
Human coagulation factor X for hereditary factor X deficiency (all ages)

Actions Requested	1. Support the policy proposition
	2. Recommend the relative priority

Proposition
Routinely Commissioned. Human coagulation factor X (FX) is recommended for adult and paediatric patients with hereditary FX deficiency only for prophylactic (long-term) treatment. Hereditary FX deficiency is an inherited bleeding disorder caused by a lack of a protein called FX, which is needed for blood to clot properly and therefore to prevent bleeding. The most severe forms of the condition can result in bleeding in the brain or gastrointestinal tract, which can be life-threatening if uncontrolled. Hereditary FX deficiency requires life-long treatment which includes preventing or stopping bleeding events. In the UK, severe FX deficiency requiring treatment is estimated to affect <1 person in 1,000,000. Human coagulation FX temporarily replaces the missing FX in people with hereditary FX deficiency. Repeated regular infusions are required for life. It is licenced for use in this indication. This policy is a resubmission to CPAG, it was previously submitted to CPAG for May and November 2018 prioritisation rounds.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the

	appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Operational Delivery Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition		
No	*Metric*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	The best available safety data comes from the 18 participants from 2 open-label, phase III studies (Ten01 and Ten03) with up

		to a 24 month follow-up, and 9 children aged less than 12 years from an open-label, phase III study (Ten02) with 26 weeks follow-up. In Ten01 and Ten03, 6 adverse events (side effects) considered possibly related to factor X treatment occurred in 2 participants. The adverse events were fatigue (x2), infusion-site erythema (x2), back pain, pre-dose infusion-site pain. In the paediatric Ten02 study, 28 adverse events were reported, of which 26/28 were mild, and none of the adverse events were considered related to human coagulation factor X treatment. The EPAR notes that the overall safety database for human coagulation factor X is very small (n=18), although given the rarity of the disease this was considered acceptable by the regulators.
11.	Delivery of intervention	

Other health metrics determined by the evidence review		
No	Metric	Summary from evidence review
1.	Treatment of bleeds success rate (subject assessed)	Participants were asked to score how successful the treatment of their bleed was, rated as ‘excellent’, ‘good’, ‘poor’ or ‘unassessable’. How each of these was defined was determined by the type of bleed (overt, covert or menorrhagic). Bleed treatments rated ‘excellent’ or ‘good’ were classified as treatment successes. Evidence from the main open-label, non-randomised, phase III study (Ten01, Austin et al. 2016) indicated that of the 187 bleeds selected by the data review committee for analysis, 184 bleeds (98.4%) were considered a treatment success by the subject (assessed as ‘excellent’ [90.9%] or ‘good’ [7.5%] response). Two bleeds (1.1%) were treatment failures (assessed as ‘poor’ response), and 1 bleed was not assessable. These results suggest that nearly all bleeds were treated successfully with human coagulation factor X from a patient perspective. These results are based on a single arm study. A study comparing Coagadex to placebo would not have been ethical and therefore there were some constraints on study design. People in this study were therefore not randomised, and treatment with human coagulation factor X has not been compared to standard therapy or no treatment. Taking into account the difficulties around patient recruitment and study design, it remains that these were open-label, non-

		comparative studies which are subject to bias. As such, other aspects may have influenced the results for this outcome.
2.	Treatment of bleeds success rate (investigator assessed)	Trial investigators scored how successful the treatment of a bleed was, rated as 'excellent', 'good', 'poor' or 'unassessable'. How each of these was defined was determined by the type of bleed (overt, covert or menorrhagic). Bleeds rated 'excellent' or 'good' were classified as treatment successes. Evidence from the main open-label, non-randomised, phase III study (Ten01, Austin et al. 2016) reported that 10 of the 16 subjects in the study visited the investigation site for assessment of their 42 bleeds. Of these, 41 bleeds (97.6%) were considered a treatment success by the investigator (assessed as 'excellent' [88.1%] or 'good' [9.5%] response). One bleed (2.4%) was a treatment failure (assessed as 'poor' response). These results suggest that nearly all bleeds were treated successfully with human coagulation factor X from an investigator's perspective. These results are based on a single arm study. A study comparing Coagadex to placebo would not have been ethical and therefore there were some constraints on study design. People in this study were therefore not randomised, and treatment with human coagulation factor X has not been compared to standard therapy or no treatment. Taking into account the difficulties around patient recruitment and study design, it remains that these were open-label, non-comparative studies which are subject to bias. As such, other aspects may have influenced the results for this outcome.
3.	Number of factor X infusions required to treat a bleed	Study investigators how many factor X infusions were required to treat each bleed. The main open-label, non-randomised phase III study (Ten01, Austin et al. 2016) reported that the mean number of factor X infusions required to treat a bleed was 1.2 (standard deviation [SD] 0.47). The mean total dose of human coagulation factor X used to treat 1 bleed was 30.4 IU/kg (SD 12.4; median 25.0; interquartile range 24.4 to 26.7 IU/kg). The standard human coagulation factor X dose of 25 IU/kg was maintained in 14/16 participants, with the remaining 2 participants treated with 30 IU/kg and 33 IU/kg. Tranexamic acid was used as an adjunct to factor X in 7 participants (43.3%). The dose used was not reported. In the Ten02 study (Liesner et al. 2018), 4 bleeds were treated

		using human coagulation factor X. Each bleed was treated with a single human coagulation factor X infusion, the mean dose was 35.3 IU/kg (SD 7.2) These results suggest that in a clinical trial setting the majority of patients can be successfully treated with the standard human coagulation factor X dose.
4.	Bleeding management during and after surgery (assessed by investigators and data review committee)	Investigators assessed how well human coagulation factor X controlled bleeding during and after surgery. This was assessed as being 'excellent' (parameters similar to person without a bleeding disorder), 'good' (parameters inferior to person without a bleeding condition, but no other factor X-containing treatment required), 'poor' (blood loss excessive and/or haemostasis not achieved and/or additional factor X-containing treatment required) or 'unassessable'. Evidence for the specialist-assessed perioperative management of bleeding comes from 2 open-label, non-randomised phase III studies (Ten01 and Ten03) reported in 1 paper (Escobar et al. 2016). Across these 2 studies a total of 5 participants underwent 7 surgical procedures (4 major procedures, 3 minor procedures). For all 7 procedures the investigators and the data review committee assessed the treatment as having 'excellent' efficacy, meaning 'parameters are similar to those in subjects without a bleeding disorder'. These results would suggest that people with hereditary factor X deficiency who received human coagulation factor X before surgery had similar bleeding parameters to people without a bleeding condition. Across the 2 studies all the major procedures were in people with mild factor X deficiency, and all the minor procedures were in people with severe deficiency. The efficacy of factor X in people with severe deficiency undergoing major surgery has not been reported in a published study. These results should be interpreted with caution as they are based on a single arm study. People in this study were not randomised, and treatment with human coagulation factor X has not been compared to standard therapy or no treatment. Other factors may have influenced the results, and it does not provide evidence that human coagulation factor X is any better or worse than other treatments for this outcome.
5.	Blood loss during and after surgery	The investigators estimated actual blood loss during surgery. This was compared with expected blood loss, based on estimated blood loss in that type of surgery in a person without a bleeding disorder. Evidence for blood loss during surgery comes from 2 open-label, non-randomised phase III studies (Ten01 and Ten03)

		reported in 1 paper (Escobar et al. 2016). Across these 2 studies a total of 5 participants underwent 7 surgical procedures (4 major procedures, 3 minor procedures). Blood loss was 'as expected' for 5 procedures and 'less than expected' in 2 procedures. These results suggest that people with hereditary factor X deficiency who received human coagulation factor X before surgery lost the same amount or blood or less blood compared to a person without a bleeding condition undergoing the same operation. Across the 2 studies all the major procedures were in people with mild factor X deficiency, and all the minor procedures were in people with severe deficiency. The efficacy of factor X in people with severe deficiency undergoing major surgery has not been reported in a published study. These results should be interpreted with caution as they are based on a single arm study. People in this study were not randomised, and treatment with human coagulation factor X has not been compared with an active comparator arm. Other aspects may have influenced the results
6.	Investigator assessment of prophylactic efficacy over 26 weeks	The effectiveness of long-term prophylaxis was assessed by the investigator over the 26-week study period. In Ten02 (Liesner et al. 2018), prophylaxis in all 9 participants was assessed as 'excellent', meaning no minor or major bleeds occurred during the study period, or there was a lower frequency of bleeds than expected given subject's medical or treatment history.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
The policy proposition supports the use of human coagulation factor X for hereditary factor X deficiency which is its licensed indication. It is excluded from tariff.

Considerations from review by National Programme of Care Board
2) The proposal received the support of the Blood & Infection PoC Board on the 13th April 2018, and again in October 2018, subject to the following comments: 1. Noting the potential of human coagulation factor X to reduce health inequalities for the target patient group. 2. Noting the uncertainty regarding future clinical practice impacting on the estimate of the number of patients treated with human coagulation factor X prophylaxis. 3. Noting the uncertainty regarding the dose conversion ratio from the current standard of care to human coagulation factor X. This concerns uncertainty

relating to factor X levels in the treatment currently used. An algorithm for calculating dose conversion to factor X is available to guide clinicians.

4. This proposal has been resubmitted to CPAG with some agreed revisions.