CPAG Summary Report for Clinical Panel – URN 1716 - Human coagulation factor X for hereditary factor X deficiency (all ages)

The Benefits of the Proposition			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [B]	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. The unpublished results from Liesner et al. (Ten02) have been taken into account by the policy working group based on a confidential draft of the article which was provided by the company. This will be published in the near future and will be available at the time a commissioning policy is considered for routine commissioning.

			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. 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. 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. These preceding data will be included in Liesner et al. (Ten02 study) but have already been presented in a conference abstract (Liesner et al. 2017) and therefore are not considered academic-in-confidence.
11.	Delivery of intervention	Choose an item.	

Other health outcome measures determined by the evidence review			
No	Outcome measure	Grade of evidence	Summary from evidence review
1.	Treatment of bleeds success rate (subject assessed)	Grade C	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 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 (including no treatment).
2.	Treatment of bleeds success rate (investigator assessed)	Grade C	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 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.
3.	Number of factor X infusions required to treat a bleed	Grade B	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. The unpublished results from Liesner et al. (Ten02) regarding the number of infusions were required to treat a bleed have been taken into account by the policy working group based on a confidential draft of the article which was provided by the company. This will be published in the near future and will be available at the time a commissioning policy is considered for routine commissioning. 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)	Grade C	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	Grade C	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 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.
6.	Investigator assessment of prophylactic efficacy over 26 weeks	C	The effectiveness of long-term prophylaxis was assessed by the investigator over the 26-week study period. In Ten02 (in publication), 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. These preceding data will be included in Liesner et al. (Ten02 study) but have already been presented in a conference abstract (Liesner et al. 2017) and therefore are not considered academic-in-confidence. The unpublished results from Liesner et al. have been taken into account by the policy working group based on a confidential draft of the article which was provided by the company. This will be published in the near future and will be available at the time a commissioning policy is considered for routine commissioning.