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Clinical evidence review of Human coagulation factor X for hereditary factor X deficiency (all ages)

NHS England Unique Reference Number 170105P / CSP ID002

First published: February 2018

Updated: [Not applicable]

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About this clinical evidence review

Clinical evidence reviews provide a summary of the best available evidence for a single technology within a licensed indication for which the responsible commissioner is NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

This evidence review considers human coagulation factor X for the treatment and prophylaxis of bleeding episodes and for perioperative management in people with hereditary factor X deficiency. The evidence review was undertaken in line with the standard operating procedure for undertaking clinical evidence reviews.

A literature search was undertaken, which identified 36 references (see appendix 1 for search strategy). The company also provided a submission of evidence. From this, 3 published studies were included in the review.

Overview of included studies

Evidence of the effect of human coagulation factor X comes from 3 open-label, single-arm, phase III studies that included a total of 27 participants (Ten01 study and Ten03 study reported in Austin et al. 2016 and Escobar et al. 2016, and Ten02 study reported in Liesner et al. 2018). An additional single case report provides some context and safety information. Please see Table 2 and Table 3 in the main report for an overview of the included studies and their results

Effectiveness

Evidence for the treatment or short-term prevention of bleeds in people aged 12 years and over comes from an open-label, single-arm, phase III study involving 16 people aged 12 years or more with moderate or severe hereditary factor X deficiency (Austin et al. 2016). Out of 187 bleeds, the response to treatment was considered excellent, good, poor or unassessable in 90.9%, 7.5%, 1.1% and 0.5% of bleeds respectively. In the 2 participants who received long-term prophylaxis the mean number of bleeds reduced from 0.23 and 0.82 bleeds per month to 0 bleeds per month.

The best evidence for the long-term prevention of bleeds comes from an open-label, single-arm, phase III study involving 9 children aged less than 12 years with moderate or severe hereditary factor X deficiency (Liesner et al. 2018). The effectiveness of prophylaxis was assessed by the investigators

over 26 weeks, after which time treatment for all 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.

Evidence for the perioperative management of bleeding is provided by 5 participants from the 2 open-label, single-arm, phase III studies (Ten01 and Ten03; reported in Escobar et al. 2016) who underwent 7 surgical procedures. For all procedures the specialists assessed the treatment as having 'excellent' efficacy and blood loss was 'as expected' or 'less than expected'.

Safety and tolerability

Across the 2 open-label, single arm, phase III studies (Ten01 and Ten03) no participants developed factor X inhibitors or thromboembolic events.

Based on the safety data from the 18 participants enrolled in the Ten01 and Ten03 studies, the SPC for Coagadex states that the following adverse reaction have been reported commonly in people treated with human coagulation factor X (occurring in ≥1/100 to <10/100 people): back pain, infusion site erythema, fatigue and infusion site pain. In the paediatric Ten02 study a total of 28 adverse events were reported in 8/9 participants, the majority of which were mild in severity. None of the adverse events were considered by the investigators to be related to the study treatment.

Evidence gaps

The published evidence base available for human coagulation factor X is limited to the treatment and prevention of bleeds in adults with moderate to severe hereditary factor X deficiency, the perioperative management of bleeds in adults with mild to severe hereditary factor X deficiency and the long-term prevention and treatment of bleeds in children aged less than 12 years.

All included studies were open-label, non-comparative trials, although the rarity of hereditary factor X deficiency limits the number of potential people for clinical trials.

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Abbreviations

Term	Definition
CVAD	Central venous access device
FFP	Fresh frozen plasma
FX	Factor X
FX:C	Factor X functional activity
IR	Incremental recovery
PCC	Prothrombin complex concentrate

Introduction

Disease background

Hereditary factor X deficiency is a rare, autosomal recessive bleeding disorder of variable severity.

Hereditary factor X deficiency can present as a mild, moderate or severe deficiency state. Mild factor X deficiency (factor X functional activity [FX:C] 6 to 10 IU/100 ml) is characterised by easy bruising or menorrhagia, and is normally identified during routine screening or from family history. Moderate factor X deficiency (FX:C 1 to 5 IU/100 ml) is associated with excessive bleeding following trauma or surgery and normally presents after such events. Severe factor X deficiency (FX:C <1 IU/100 ml) may present in neonates, often with central nervous system or umbilical-stump bleeding, and tends to exhibit the most severe phenotype. Factor X deficiency can be further divided into 2 forms, type I deficiency (low factor X activity and low antigen levels) and type II deficiency (low factor X activity and normal antigen levels) (Shapiro 2017).

Intracranial bleeding (bleeding inside the skull, in and around the brain) and umbilical bleeding (from where the belly button cord was cut) may be one of the first symptoms of hereditary factor X deficiency in infants (Peyvandi & Mannucci, 1999; Acharya et al, 2004; Herrmann et al, 2006). Factor X activity has a broad range in healthy infants and increases over the next 6 months (Andrew et al, 1987). Therefore, diagnosis of factor X deficiency at birth requires comparison of test results with reference levels or testing after routine administration of vitamin K1, and, if necessary confirmation at re-testing at 6 months of age (Mumford et al. 2014).

Some adults with hereditary factor X deficiency do not need routine treatment. They will, however, require treatment for planned surgery (including dental work). Some people with hereditary factor X deficiency avoid leading active lives (including sports) due to the condition. Holstein et al. (2015) assessed the impact of social status and disease-related impairment of certain aspects of patients with haemophilia. The study reported that haemophilia had an

impact on more than half of the patients (n=57), particularly on their school education, childhood and leisure activities. Patients with a high impact of haemophilia on their lives were less satisfied with their lives ($P < 0.002$) and reported worse a quality of life. (Holstein et al. 2015)

Treatments for hereditary factor X deficiency often involve the replacement of factor X. Historically this has been achieved using fresh frozen plasma (FFP) or non-specific plasma-derived products, for example prothrombin complex concentrate (PCC) that also contain other clotting factors (Shapiro 2017). Hereditary factor X deficiency requires life-long treatment which includes preventing or stopping bleeding events.

Infants and children with hereditary factor X deficiency often require a central venous access devices (CVADs) which facilitates venous access. CVADs are routinely used in infants and young children to allow easy treatment administration but having a CVAD increases the risk of thrombosis. In addition to the known increased risk of thrombosis associated with it, the use of PCCs is more likely to block a CVAD than a factor X concentrate as it has activated forms of the coagulation factor proteins which can initiate clotting (Khair et al. 2014).

Human coagulation factor X is the first product that contains only factor X that is specifically licensed for the management of hereditary factor X deficiency.

Epidemiology

Hereditary factor X deficiency has a prevalence of 1:500,000 to 1:1,000,000 of the general population (Austin et al. 2016).

In the company submission, Bio Products Laboratory Limited state that the World Federation of Haemophilia (WFH) estimates the number of people worldwide with hereditary factor X deficiency is 1,655, of which 216 people (13%) live in the UK. A relatively high number of people with hereditary factor X deficiency also live in Ireland (123 people), the USA (101 people) and Italy (96 people).

In their patient and carer organisation submission, the Haemophilia Society state that only 35 people (14.5%) in the UK diagnosed with hereditary factor X deficiency received treatment in a year.

Table 1 Patient numbers

Registered on UK Haemophilia Database	Total people	Actual number of patients requiring treatment from April 2015 to March 2016 (%)
People with hereditary factor X deficiency (all severities)	241	35 (14.5%)
People with moderate hereditary factor X deficiency (FX:C≥ 5 IU/100 ml)	37	25 (67.5%)
People with severe hereditary factor X deficiency (FX:C< 5 IU/100 ml)	204	10 (0.5%)

Product overview

Mode of action

Human coagulation factor X temporarily replaces missing factor X in people with hereditary factor X deficiency to achieve haemostasis.

Regulatory status

Human coagulation factor X is licensed for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency (summary of product characteristics [SPC]: Coagadex).

Dosing information

The dose and duration of treatment with human coagulation factor X on the severity of the factor X deficiency, on the location and extent of the bleeding and on the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes. Not more than 60 IU/kg daily should be administered. The SPC starts that the dose and duration of treatment in adults and children are the same, but the safety and efficacy of human coagulation factor X in children less than 12 years of age has not yet been established (SPC: Coagadex).

Control and prevention of bleeding episodes

For treatment of bleeding episodes: 25 IU/kg human coagulation factor X should be injected when the first sign of bleeding occurs or just before the expected onset of menstrual bleeding, and repeated at intervals of 24 hours until the bleed stops. Each individual bleed should be judged on its own severity.

For secondary prophylaxis against re-bleeding or short-term prophylaxis prior to anticipated physical activity or dental appointments: 25 IU/kg human coagulation factor X should be injected and repeated as required.

There are limited data on the use of human coagulation factor X for longer periods of prophylaxis but 24.6 to 28 IU/kg once weekly or 25 IU/kg every 2 weeks have been used for several weeks or months (SPC: Coagadex).

Perioperative management

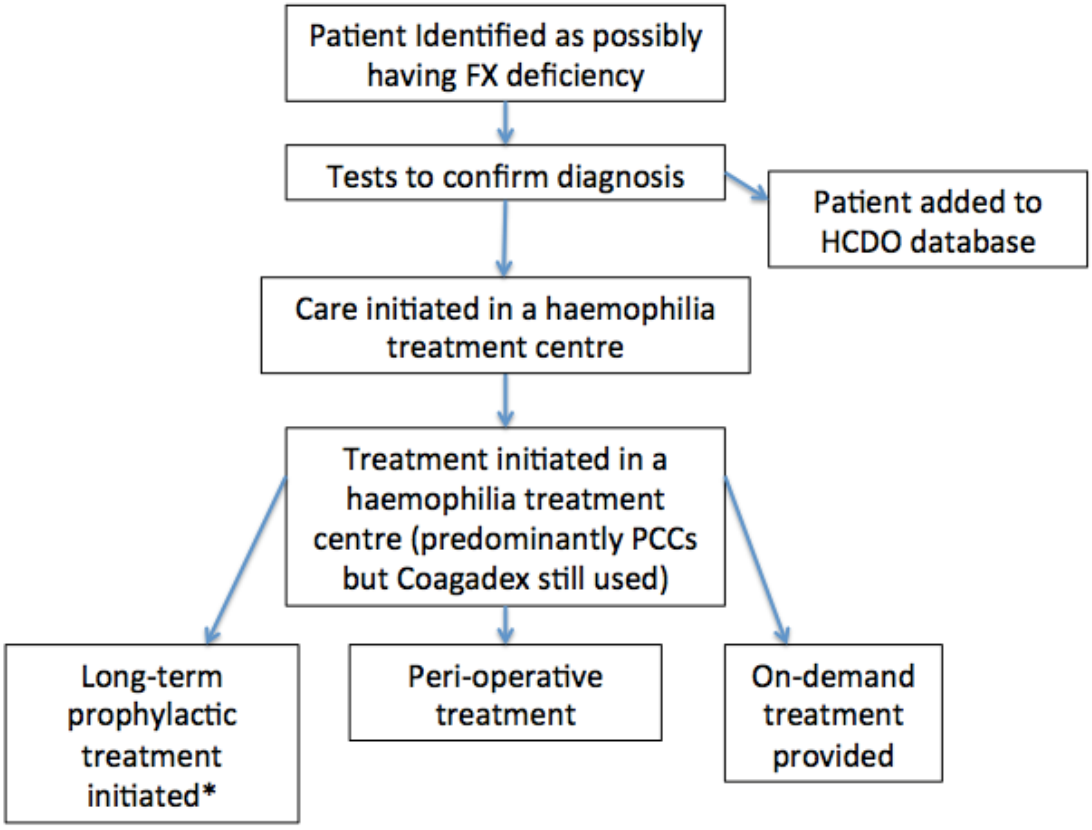
Pre-surgery, the dose of human coagulation factor X should be calculated to raise plasma factor X levels to 70–90 IU/100 ml. The careful control of dose and duration of treatment is especially important in cases of major surgery (SPC: Coagadex).

Treatment pathway and current practice

Factor X replacement therapy is appropriate for people with hereditary factor X deficiency who are bleeding or are at risk of bleeding.

In the company submission, Bio Products Laboratory Limited provided the following treatment pathway:

Figure 1. Current pathway of care in England



* PCCs not licensed for long-term prophylaxis

Prothrombin complex concentrate (PCC), the current treatment option used in the UK for people with hereditary factor X deficiency, contains factor II, VII, IX, and X. The half-lives of the coagulation factors differ considerably (factors II - 60 hours, factor X – 30 hours, factor IX - 20 hours and factor VII - 6 hours). Patients with hereditary factor X deficiency have usual levels of the other factors which are included in PCCs. As a consequence, repeated dosing will lead to an accumulation of these other unneeded factors, which can lead to an increased risk of thrombosis (blood clots) (Beriplex and Octaplex summary of product characteristics).

PCCs do not contain a standard amount of factor X in each vial which means that dosing requirements are unpredictable and there is a risk of under or over dosing. Since the factor X content can vary by as much as 2-3 times between batches of PCC, factor X levels need to be closely monitored which may

require additional blood tests (Beriplex and Octaplex summary of product characteristics).

Because PCCs contain other factors, the volumes of PCC needed to achieve haemostasis (normal levels of blood clotting) are large and can be too large for infants and children. Infusion with PCCs can take between 8 and 70 minutes depending on the PCC and required dose. A single dose of PCC to replace factor X typically involves injection of at least 20 ml of fluid which in infants and young children is a large volume to safely inject into a small peripheral vein. Administration of PCC sometimes has to be split over 2 or 3 clinic visits.

Innovation and unmet need

Human coagulation factor X (Coagadex) is the first product containing only factor X for the management of factor X deficiency.

In their company submission, Bio Products Laboratory Limited highlighted that the European Medicines Agency (EMA) listed Coagadex in their Human medicines highlights 2016 as 1 of 6 innovations advancing public health. Prior to the approval of human coagulation factor X (Coagadex), there were no specific treatments licensed for hereditary factor X deficiency in the EU.

The company state that current treatment with PCCs can lead to safety and efficacy concerns due to the potential off-target effects of other coagulation factors also present in PCCs. PCCs contain factor X along with other factors, and the content of each factor can vary considerably between products. Clinicians estimate the amount of factor X in a dose based on historic ratios measured in the product.

There may also be practical limitations of treating people with PCCs, because those requiring higher doses may need to split their treatment over 2 or 3 visits. A single infusion of human coagulation factor X can be given in minutes, whereas PCCs (such as Beriplex and Octaplex) require an infusion duration of at least 8 minutes 45 seconds, and 25 to 70 minutes, respectively.

In addition to on-demand treatment, patients with severe factor X deficiency may require prophylactic treatment. The company state that human coagulation factor X is a more suitable treatment option than PCC for prophylaxis, due consistent factor X dosing, the option for patients to infuse their treatment at home and a smaller chance of volume overload in repeated infusions.

The company's comments are supported by the patient organisation submission, which stated: "*There is no other factor X concentrate available in the UK and this has a significant impact on the quality of life for those with a diagnosis. Current treatments are generic, not focussed on delivering factor X and members tell us they are not particularly effective. This is particularly the case for people with the severe form, or women who have heavy menstrual bleeding*."

Equality

In their company submission, Bio Products Laboratory Limited state that factor X deficiency remains the only patient group with a bleeding condition where access to a pure replacement clotting factor is limited. This is explicitly expressed by a patient in their statement on the treatment of their factor X deficiency "*This makes me feel that by having Factor X deficiency I am at a disadvantage, as there is more choice in treatment for other inherited factor deficiencies*."

The company also states that there are concerns around the equality of treatments for hereditary rare blood coagulation disorders across different cultures. Conditions such as factor X deficiency are more likely to occur in cultural groups where consanguinity is more common. Most affected individuals in the UK are likely to be of Asian or Muslim background. Therefore, any inequality in treatment of this group compared to other genetic disorders may be perceived as discriminatory.

Evidence review

Identification of studies

The review was done in line with the methods for carrying out clinical evidence reviews.

A literature search was done, which identified 36 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 18 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and 2 studies were included in the clinical evidence review (see appendix 2 for inclusion/exclusion criteria and a list of studies excluded at full text with reasons).

The company submission identified 9 references to published studies in their submission. Eight of these studies were identified in the literature search, and as such 1 additional unique reference was identified (Kumar et al. 2014). An additional study was published after the literature search was completed and has been included in the evidence review (Liesner et al. 2018 [Ten02]).

As such, 4 studies met the inclusion criteria and were subsequently included. Please note, the European public assessment report (EPAR) for human coagulation factor X (Coagadex) was also used to supplement the published data.

Results

Overview of included studies

The best evidence for the treatment and short-term prophylaxis of bleeds comes from 1 open-label, non-randomised, phase III study involving 16 participants (Austin et al. 2016 [Ten01]). Evidence for perioperative management of bleeding comes from another open-label, non-randomised phase III study involving 2 participants who underwent 2 procedures each (Ten03). The results of Ten03, and the outcomes for 3 participants from the Ten01 study who each underwent 1 surgical procedure are reported by

Escobar et al. (2016). Evidence for the long-term prophylaxis and treatment of bleeds in children aged less than 12 years comes from 1 open-label, non-randomised, phase III study involving 9 participants (Liesner et al. 2018 [Ten02]).

A summary of the characteristics of the included studies is shown in table 2. The more detailed evidence tables and results tables can be found in appendices 4 and 5. See appendix 5 for the details of the methods for grading evidence using the National Service Framework Long-term Conditions tool (NSF-LTC).

Table 2 Summary of included studies

Study	Population	Intervention and comparator	Follow-up
Ten01 study Reported in Austin et al. (2016) Open-label, single-arm, phase III study	16 people aged 12 years and over with moderate or severe hereditary factor X deficiency (FX:C <5 IU/100 ml) with 1 or more bleeds requiring factor X replacement in the previous 12 months The median age of the participants was 20 years and 10/16 participants were female. At baseline 2/16 participants were classified as having moderate deficiency and 14/16 participants as having severe deficiency (FX:C <1 IU/dL)	Human coagulation factor X (Coagadex) 25 IU/kg No comparator	Up to 24 months
Ten03 study Reported in Escobar et al. (2016) Open-label, single-arm, phase III study	2 people aged 12 years and over with mild to severe hereditary factor X deficiency (FX:C <20 IU/100 ml) who were undergoing surgery (4 procedures in total)	Human coagulation factor X (Coagadex) dosed to raise FX:C to 70–90 IU/100 ml pre-operatively and ≥50 IU/100 ml in the post-operative period No comparator	Up to 24 months
Ten02 study Liesner et al. (2018) Open-label, single-	9 children aged less than 12 years with moderate or severe hereditary factor X deficiency (basal plasma factor X activity <5 IU/dL), and history of severe bleeding or an	Human coagulation factor X. Dosed to maintain FX:C above 5 IU/dL	26 weeks

Study	Population	Intervention and comparator	Follow-up
arm, phase III study	F10 gene mutation known to cause a severe bleeding phenotype. Five out of 9 participants were female. Eight participants had severe factor X deficiency (FX:C <1 IU/dL), and 1 participant had moderate deficiency (FX:C (≥1 to <5 IU/dL).	No comparator	
Kumar et al. 2014 Single patient case study	Case study of a 9 year old girl with severe hereditary factor X deficiency and a history of central venous access device blockage following long-term prophylaxis with PCC	Human coagulation factor X (Coagadex) No comparator	Case study reports on 3 years treatment

Overview of key results

Table 2 below provides a grade of evidence summary of the outcomes identified in the scope. The key outcomes are discussed below for effectiveness and safety.

Effectiveness

Treatment of bleeds

Evidence from an open-label, single arm, phase III study involving 16 people with moderate or severe hereditary factor X deficiency found that nearly all bleeds treated with human coagulation factor X were considered 'treatment successes' (Ten01, Austin et al. 2016; moderate quality evidence). The mean age of the participants was 20 years and 10/16 participants were female. At baseline 2/16 participants were classified as having moderate deficiency and 14/16 participants as having severe deficiency.

The study used 2 methods for assessing treatment success: subject assessment and investigator assessment. Of the 187 analysed bleeds, the subjects assessed their response to treatment as 'excellent' for 170 bleeds (90.9%) and 'good' for 14 bleeds (7.5%). Two bleeds (1.1%) were assessed as a 'poor' response and considered treatment failures, and 1 bleed was not assessable. The investigators assessed response to treatment in 42 bleeds in

10/16 participants. In total, 37 bleeds (88.1%) were assessed as having an 'excellent' response to treatment and 4 bleeds (9.5%) a good response. One bleed (2.4%) had a 'poor' response and was considered a treatment failure.

In the Ten01 study, the mean number of factor X infusions required to treat a bleed was 1.2 (standard deviation [SD] 0.47), with a mean total dose to treat a bleed of 30 IU/kg (SD 12.4). Tranexamic acid was used as adjunctive therapy in 7/16 of participants (43.3%).

The Ten02 study is an open-label, phase III, single-arm study involving 9 children aged less than 12 years with moderate or severe factor X deficiency (Liesner et al. 2018). The study focused on the prophylaxis of bleeds. Over the 26 week study period there were 10 bleeding events occurring in 3 participants. Six bleeds were classed as minor, 3 bleeds were major and in 1 bleed the severity was not recorded.

Prevention of bleeds

Across the 16 participants enrolled in the Ten01 study a total of 184 preventative dose of human coagulation factor X were administered to 9 participants (EPAR: Coagadex; moderate quality evidence). Of these, 56 infusions (30.4%) were given as secondary prophylaxis to prevent re-bleeding and 45 infusions (24.5%) were given as short-term prophylaxis, for example before a sporting event. In addition, 57 infusions (31.0%) were given as routine prophylaxis to 2 participants; the Ten01 study was not designed to investigate long-term prophylaxis and this constituted a protocol deviation. The remaining 26 infusions (14%) were administered for a number of reasons, including dental visits and prophylaxis of rectal bleeding. The mean number of preventative infusions per participant per month was 1.62, with a mean dose of 25.24 IU/kg per person.

The EPAR reports that in the 2 participants who received long-term prophylaxis with human coagulation factor X the mean number of bleeds reduced from 0.23 and 0.82 bleeds per month when not on treatment to 0 bleeds per month when receiving infusions.

Efficacy results for the participants who received secondary prophylaxis or short-term prophylaxis are not reported by in Austin et al. (2016) or in the EPAR. It is not clear why these results are not reported, although the lack of control in the study and the wide range of indications for prophylaxis may prevent meaningful results being extracted.

The Ten02 study investigated the prophylactic efficacy of human coagulation factor X in children aged less than 12 years with moderate or severe factor X deficiency (n=9; Liesner et al. 2018). Investigators rated overall human coagulation factor X efficacy as excellent in all subjects.

Perioperative management of bleeding

Evidence for the use of human coagulation factor X for the perioperative management of bleeding is provided by 5 participants from the 2 open-label, single-arm, phase III studies (Ten01 and Ten03) who underwent 7 surgical procedures (Escobar et al. 2016; moderate quality evidence).

For all 7 procedures specialists assessed the treatment as having 'excellent' efficacy. Blood loss was 'as expected' for 5 procedures and 'less than expected' in 2 procedures, and no participants required a blood transfusion. Although some changes in haemoglobin and haematocrit levels were observed, these were not considered clinically significant by the investigators.

Safety and tolerability

Across the 3 open-label, single arm, phase III studies (Ten01, Ten02 and Ten03) no participants developed factor X inhibitors or thromboembolic events (moderate quality evidence).

The Ten01 study that investigated the treatment and prevention of bleeds in 16 people found that headache was the most common adverse event, occurring in 8 subjects. The investigators note the all headache events were mild and not thought to be related the study drug. In total, 6 adverse events that occurred in 2 participants were considered by the investigators to be related to treatment with human coagulation factor X.

Based on the safety data from the 18 participants enrolled in the Ten01 and Ten03 studies, the SPC for Coagadex states that the following are common adverse reaction (occurring in 10/100 to 1/100 people): back pain, infusion site erythema, fatigue and infusion site pain.

In the paediatric Ten02 study that investigated long-term prophylaxis, a total of 28 adverse events were reported in 8/9 participants; none were considered human coagulation factor X related.

A case study by Kumar et al. (2014) describes the case of a 9 year old girl with severe hereditary factor X deficiency who required regular factor X-based prophylaxis. The child was receiving twice weekly doses of PCC via a central venous access device (CVAD). Infusion occlusion occurred 2 years after insertion of the CVAD (the child's fifth), meaning the PCC could no longer be given intravenously. PCC prophylaxis was attempted peripherally but was complicated by journey times to and from hospital. A decision was made to switch the child to human coagulation factor X (Coagadex), initially administered peripherally, then via a new CVAD. The case study reported that treatment with human coagulation factor X was continued at home for 3 years with no adverse complications, and the CVAD remained in situ with no infusion issues.

Evidence gaps

The published evidence base available for human coagulation factor X provides information on the treatment and short-term prevention of bleeds in people aged 12 years or more with moderate to severe hereditary factor X deficiency, the perioperative management of bleeds in people aged 12 years or more with mild to severe deficiency and the long-term prevention and treatment of bleeds in children aged less than 12 years with moderate to severe deficiency.

Comparative studies

None of the included studies compared human coagulation factor X with other treatments for hereditary factor X deficiency, for example PCC. None of the included studies had control arms. However, since hereditary factor X

deficiency is a very rare condition the potential number of participants for clinical trials is limited, as noted by the regulators in the EPAR. In addition to this, the summary of product characteristics for the PCCs Beriplex and Octaplex state that these products are only licensed for the treatment and perioperative prophylaxis of bleedings in congenital deficiency of any of the vitamin K dependent coagulation factors when purified specific coagulation factor products are not available.

Key ongoing studies

The Ten06 study is an ongoing multicentre, post-marketing registry study of human coagulation factor in the perioperative management of patients with moderate or severe hereditary factor x deficiency undergoing major surgery, with an estimated completion date of December 2021 (NCT03161626).

Table 2 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
Treatment of bleeds success rate (subject assessed)	Ten01 (Austin et al. 2016)	6/10	Directly applicable	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).

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
Treatment of bleeds success rate (investigator assessed)	Ten01 (Austin et al. 2016)	6/10	Directly applicable	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.
Number of factor X infusions required to	Ten01 (Austin et al. 2016)	6/10	Directly applicable	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

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
treat a bleed	Ten02 (Liesner et al. 2018)	6/10	Directly applicable		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, 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.
Bleeding management during and after surgery (assessed by investigators and data review committee)	Ten03 and surgical patients from Ten01 (Escobar et al. 2016)	5/10	Directly applicable	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

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
					(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 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.
Blood loss during and after surgery	Ten03 and surgical patients from Ten01 (Escobar et al.	5/10	Directly applicable	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

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
	2016)				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 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.
Investigator assessment of prophylactic efficacy over 26 weeks	Ten02 (Liesner et al. 2018)	6/10	Directly applicable	C	The effectiveness of long-term prophylaxis was assessed by the investigator over the 26-week study period. Prophylaxis in all 9 participants was assessed as 'excellent'.
Safety – adverse	Ten01 (Austin et al.	6/10	Directly applicable	B	The best available safety data comes from the 18 participants aged 12 years and over, 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

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
events	2016)				from an open-label, phase III study (Ten02) with 26 weeks follow-up. Across Ten01 and Ten03, 6 adverse events 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, and none were considered related to human coagulation factor X treatment.
	Ten03 and surgical patients from Ten01 (Escobar et al. 2016)	5/10	Directly applicable		
	Ten02 (Liesner et al. 2018)	6/10	Directly applicable		

Relevance to guidelines and NHS England policies

NHS England and NICE have not issued any guidelines or policies on managing hereditary factor X deficiency with human coagulation factor X.

Human coagulation factor X (Coagadex) is not routinely commissioned by NHS England for hereditary factor X deficiency.

References

Austin SK, Kavakli K, Norton M et al. (2016) Efficacy, safety and pharmacokinetics of a new high-purity factor X concentrate in subjects with hereditary factor X deficiency. Haemophilia 22: 419–25

Escobar MA, Auerswald G, Austin SK et al. (2016) Experience of a new high-purity factor X concentrate in subjects with hereditary factor X deficiency undergoing surgery. Haemophilia 22: 713–20

Khair K., Kumar P., Mathias, M., et al. (2014) Successful use of BPL Factor X concentrate in a child with severe factor X deficiency. The Journal of Haemophilia Practice 1(2): 8–10

Liesner R, Akanezi C, Norton M et al. (2018) Prophylactic treatment of bleeding episodes in children <12 years with moderate to severe hereditary factor X deficiency (FXD): Efficacy and safety of a high-purity plasma-derived factor X (pdFX) concentrate. Haemophilia. Published first online 10.1111/hae.13500

Liesner R, Gattens M, Akanezi C et al. (2017) Efficacy, Safety, and Pharmacokinetics of a High-purity Plasma-derived Factor X (pdFX) Concentrate in the Prophylaxis of Bleeding Episodes in Children < 12 Years with Moderate to Severe Congenital Factor X Deficiency (FXD). Abstract presented at the 2017 International Society on Thrombosis and Hemostasis Congress, Berlin, Germany

About this clinical evidence review

Clinical evidence reviews provide a summary of the best available published evidence for a single technology within a licensed indication that falls under the remit of NHS England's specialised commissioning. The clinical evidence review supports NHS England in producing specialised commissioning policies but are **not NICE guidance or advice**.

Expert advisers

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Declarations of interest

No relevant interests declared.

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Appendix 1 Search strategy

Databases

Database: Ovid MEDLINE(R) Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
Platform: Ovid
Search date: 31 July 17
Number of results retrieved: 8
Search strategy:

1 Factor X Deficiency/ (474)
2 ("stuart prower" or stuart-prower).tw. (44)
3 (deficien* adj3 (FX or "factor X" or "factor-X" or "factor 10" or "factor-10" or "F10")).tw. (487)
4 (FX deficien* or FX-deficien* or "F10 deficien*" or "F10-deficien*").tw. (124)
5 (factor X deficien* or "factor-X deficien*" or "factor 10 deficien*" or "factor-10 deficien*").tw. (375)
6 or/1-5 (677)
7 coagadex.tw. (1)
8 (human coagulation adj (FX or "factor X" or "factor-X" or "F10" or "factor 10" or "factor-10")).tw. (24)
9 (("plasma-derived" or "plasma derived") adj (FX or "factor X" or "factor-X" or "F10" or "factor 10" or "factor-10")).tw. (7)
10 pdFX.tw. (4)
11 (purity adj (FX or "factor X" or "factor-X" or "F10" or "factor 10" or "factor-10")).tw. (3)
12 or/7-11 (31)
13 6 and 12 (8)

Database: Embase
Platform: Ovid
Version: 1974 to 2017 July 28>
Search date: 31 July 17
Number of results retrieved: 32
Search strategy:
---
1 blood clotting factor 10 deficiency/ (718)
2 ("stuart prower" or stuart-prower).tw. (34)
3 (deficien* adj3 (FX or "factor X" or "factor-X" or "factor 10" or "factor-10" or "F10")).tw. (743)
4 (FX deficien* or FX-deficien* or "F10 deficien*" or "F10-deficien*").tw. (242)
5 (factor X deficien* or "factor-X deficien*" or "factor 10 deficien*" or "factor-10 deficien*").tw. (516)
6 or/1-5 (1003)
7 coagadex.tw. (4)
8 blood clotting factor 10 concentrate/ (20)
9 (human coagulation adj (FX or "factor X" or "factor-X" or "F10" or "factor 10" or "factor-10")).tw. (34)

10 (("plasma-derived" or "plasma derived") adj (FX or "factor X" or "factor-X" or "F10" or "factor 10" or "factor-10")).tw. (15)
11 pdFX.tw. (9)
12 (purity adj (FX or "factor X" or "factor-X" or "F10" or "factor 10" or "factor-10")).tw. (19)
13 or/7-12 (75)
14 6 and 13 (38)
15 limit 14 to human (32)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:

CDSR 7 of 12, July 2017
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL –7 of 12, July 2017
HTA 4 of 4, Oct 2016
NHS EED – 2 of 4, April 2015 (legacy database)

Also browsed issues 7, 6 and 5 due to ongoing problems with Cochrane
http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/table-of-contents/2017/Issue7/

Search date:
Number of results retrieved: CDSR – 0; DARE – 0; CENTRAL – 6; HTA – 0; NHS EED – 0.
Search strategy:

Search Name: CSP Coagadex July 17

ID	SearchHits	
#1	coagadex	0
#2	(FX or "factor X" or "factor-X" or "F10" or "factor 10" or "factor-10") near/5 (human coagulation)	1
#3	("plasma-derived" or "plasma derived") near/5 (FX or "factor X" or "factor-X" or "F10" or "factor 10" or "factor-10")	5
#4	purity near/5 (FX or "factor X" or "factor-X" or "F10" or "factor 10" or "factor-10")	3
#5	pdFX:ti,ab,kw	2
#6	#1 or #2 or #3 or #4 or #5	6

Trials registries

Clinicaltrials.gov

Search date: 2 Aug 17
Number of results retrieved: 4 = (registry plus three phase III)
Search strategy and link to results page: Coagadex and Factor X:
https://clinicaltrials.gov/ct2/results?term=coagadex&cond=Factor+X+Deficiency
human coagulation factor X and Factor X deficiency:
https://clinicaltrials.gov/ct2/results?cond=Factor+X+Deficiency&term=human+coagulation+factor+X&cntry1=&state1=&Search=Search

Clinicaltrialsregister.eu

Search date: 2 Aug 17
Number of results retrieved:
Search strategy and link to results page: coagadex
https://www.clinicaltrialsregister.eu/ctr-search/search?query=coagadex human coagulation factor X: https://www.clinicaltrialsregister.eu/ctr-search/search?query=%22human+coagulation+factor+X%22

Appendix 2 Study selection

The search strategy presented in Appendix 1 yielded 36 studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria.

Sifting criteria	Inclusion	Exclusion
Population	People with hereditary factor X deficiency	Non-humans Studies on acquired factor X deficiency
Intervention	Human coagulation factor X (Coagadex)	
Comparator	Any	
Outcomes	N/A	
Other		Abstracts Non-English language Duplicates Opinion pieces, commentaries, epidemiological studies, burden of disease studies

Eighteen full text papers were ordered and assessed based on the following inclusion/exclusion criteria.

Sifting criteria	Inclusion	Exclusion
Population	People with hereditary factor X deficiency	Non-humans Studies on acquired factor X deficiency
Intervention	Human coagulation factor X (Coagadex)	
Comparator	Any	
Outcomes	See scope	
Other		Abstracts Non-English language Duplicates Opinion pieces, commentaries, epidemiological studies, burden of disease studies

The company submission identified 9 references to studies in their submission. Six of these studies were included in the database searches, and 3 additional unique references were identified. Two of these unique references were excluded

Table 3 Studies excluded at full text.

Study reference	Reason for exclusion
Alvarez M T, Fernandez I, Luddington R, Norton M, and Dash C (2010) First in human clinical experience of a high purity factor X concentrate. Blackwell Publishing Ltd	Abstract only
Alvarez M, Auerswald G, Austin S, Bermejo N, Kavakli K, Oner A, Pavord S, Macdonald S, Aldwinckle T, and Norton M (2012) Pharmacokinetics, safety, and efficacy of a high purity factor X in patients with severe and moderate hereditary factor X deficiency. Blackwell Publishing Ltd	Abstract only
Auerswald G, and Norton M (2016) Experience of a high-purity factor X concentrate in a patient with severe factor X deficiency. 60th Annual Meeting of the German Society of Thrombosis and Haemostasis Research. Germany. 36, A72-A73	Abstract only
Auerswald G and Bührlen M (2017) Pregnancy and delivery experiences in a patient with severe factor x (fx) deficiency treated with a high-purity plasma-derived factor x (pdfx) concentrate. Research and Practice in Thrombosis and Haemostasis S1: 371	Abstract only
Austin S, Alvarez M T, Auerswald G, Bermejo N, Kavakli K, Mitchell W, Oner A, Pavord S, Macdonald S, Norton M, and Aldwinckle T (2014) Pharmacokinetics of a new high purity factor X concentrate in subjects with severe or moderate factor X deficiency. Blackwell Publishing Ltd	Abstract only
Austin SK, Brindley C, Kavakli K et al. (2016b) Pharmacokinetics of a high-purity plasma-derived factor X concentrate in subjects with moderate or severe hereditary factor X deficiency. Haemophilia 22: 426–32	Paper reporting pharmacokinetic data from an included study (Ten01)
Escobar M, Millar C, Austin S, Auerswald G, Macdonald S, Norton M, and Aldwinckle T (2014) Safety and efficacy of a new high purity factor X concentrate in subjects with factor X deficiency undergoing surgery. Blackwell Publishing Ltd	Abstract only

Kavakli K, Austin S, Alvarez M T, Auerswald G, Bermejo N, Mitchell W, Oner A, Pavord S, Macdonald S, Norton M, and Aldwinckle T (2014) Efficacy and safety of a new high purity factor X concentrate in the treatment of severe or moderate factor X deficiency. Blackwell Publishing Ltd	Abstract only
Kavakli KO AF, Celkan T, Timur C, et al. (2016) Use of a high-purity factor X (FX) concentrate in six Turkish patients with hereditary FX deficiency. Haemophilia 22: S2	Abstract only
Kumar P, Liesner R, Efford J, Henderson L, Mathias M, and Khair K (2012) The successful use of human coagulation factor x concentrate (BPL) in a child with severe factor X deficiency. Blackwell Publishing Ltd	Abstract only
Martin-Salces M, Alvarez-Roman M T, Rodriguez-Merchan E C, and Jimenez-Yuste V (2013) Femur fracture in a woman with severe factor X deficiency - an experience using factor X concentrate in surgery. Blackwell Publishing Ltd (9600 Garsington Road, Oxford OX4 2XG, United Kingdom)	Not a relevant study (letter to editor)
Mikovic D (2017) Factor X constitutional deficiencies: Diagnostic and therapeutic challenges. Blackwell Publishing Ltd	Abstract only
Mitchell M, Kavakli K, Norton M, and Austin S (2015) Genotype analysis of patients with hereditary factor X deficiency enrolled in 2 phase 3 studies of PDFX, a new high-purity factor X concentrate. American Society of Hematology	Abstract only
Norton M, Mitchell W B, Alvarez M T, Austin S, Auerswald G, Bermejo N, Escobar M, Kavakli K, Millar C, Oner A, Pavord S, Macdonald S, and Aldwinckle T (2014) Safety of a new high purity factor X concentrate in the management of hereditary factor X deficiency. Blackwell Publishing Ltd	Abstract only
Peyvandi F (2015) Emerging therapies for rare bleeding disorders-FV, FX. Blackwell Publishing Ltd	Abstract only
Peyvandi F, Garagiola I, and Biguzzi E (2016) Advances in the treatment of bleeding disorders. Blackwell Publishing Ltd (E-mail: customerservices@oxonblackwellpublishing.com)	Not a relevant study (review article)
Shapiro A (2017) Plasma-derived human factor X concentrate for on-demand and perioperative treatment in factor X-deficient patients: pharmacology, pharmacokinetics, efficacy, and safety. Taylor and Francis Ltd (E-mail:	Not a relevant study (review article)

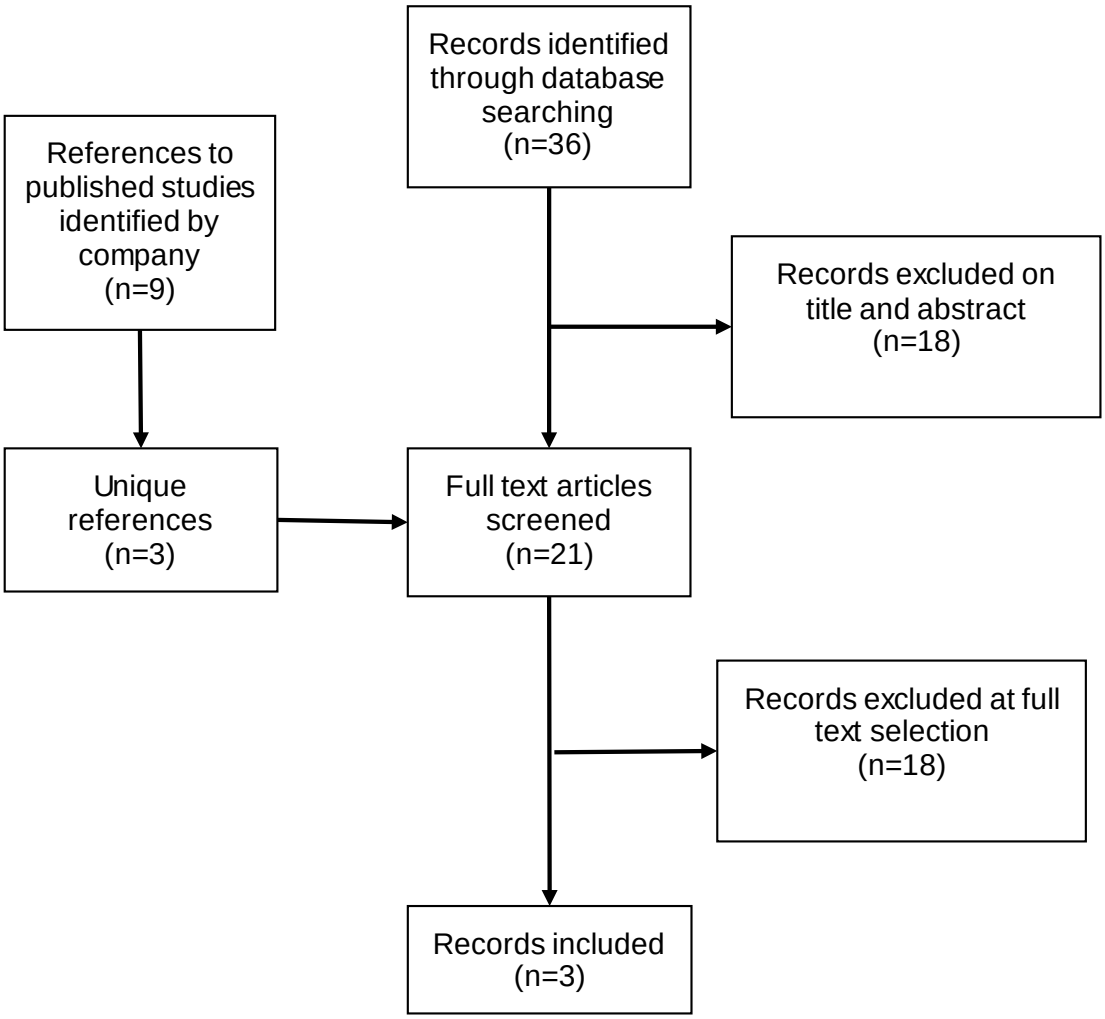
healthcare.enquiries@informa.com)	
Zhao X J, Zhou L M, and Zhao Y H (2016) First orphan drug for hereditary factor X deficiency: coagadex. Chinese Journal of New Drugs Co. Ltd.	Non-English language study

The company also provided data for 1 unpublished study which was not selected for inclusion.

As such, 3 studies met the inclusion criteria and were subsequently included.

Please note, the EPAR was also used to supplement the published data from the 2 open-label, phase III studies (Ten01 and Ten02).

Figure 1 Flow chart of included studies



Appendix 3 Evidence tables

Table 4 Ten01 study (Austin et al. 2016)

Study reference	Austin SK, Kavakli K, Norton M et al. (2016) Efficacy, safety and pharmacokinetics of a new high-purity factor X concentrate in subjects with hereditary factor X deficiency. Haemophilia 22(3): 419–25
Unique identifier	NCT00930176
Study type	Open label, non-randomised phase 3 study (P1 Primary research using quantitative approaches)
Aim of the study	To evaluate the efficacy and safety of human coagulation factor X for the treatment of bleeding episodes in people aged 12 years and over with moderate or severe hereditary factor X deficiency.
Study dates	February 2010 to October 2013
Setting	Germany (1 centre), Spain (2 centres), Turkey (6 centres), United Kingdom (2 centres) and United States (3 centres)
Number of participants	16 participants enrolled and received treatment
Population	People aged 12 years and over (median age 20 years [range 12 to 58]; 63% female) with moderate or severe hereditary factor X deficiency (basal plasma factor X activity <5 IU/100 ml).
Inclusion criteria	Basal plasma factor X activity <5 IU/100 ml Required replacement therapy (fresh-frozen plasma, prothrombin-complex concentrates or products containing factor IX and factor X) concentrate) for ≥1 spontaneous or menorrhagic bleeds in the past 12 months
Exclusion criteria	History of factor X inhibitor development Positive for factor X inhibitors at screening Thrombocytopaenic at screening Clinically significant renal or liver disease Presence of another coagulopathy or known thrombophilia
Intervention(s)	Human coagulation factor X 25 IU/kg infused at a rate of 20 mL/min or slower. For the treatment of a bleed this dose could be repeated as necessary until haemostasis was achieved.
Comparator(s)	None (single-arm study)
Length of follow-up	Up to 24 months (mean follow-up 13.9 months)
Outcomes	Primary outcomes: • Pharmacokinetics following single dose: o Factor X functional activity (FX:C) incremental recovery (IR) during 60 minutes post-dose

	o FX:C half-life
	Secondary outcomes: • Subject's assessment of efficacy (all bleeds), rated as 'excellent', 'good', 'poor' or 'unassessable' (see rating scales for individual types of bleed below) • Subjects assessment of efficacy (overt bleeds), using the following rating scale: o Excellent: Bleeding stopped within 12 hours after dosing with factor X, with only 1 dose required o Good: Bleeding stopped within 24 h after the first dose of factor X, with 1 or 2 doses required o Poor: Bleeding stopped later than 24 h after the first dose of factor X; or more than 2 doses of factor X were required; or factor X did not work at all o Unassessable: Person did not take any factor X for this bleed; or prior to taking factor X for this bleed, the patient had taken a dose of fresh-frozen plasma, prothrombin complex concentrate or factor IX/X concentrate • Subjects assessment of efficacy (covert bleeds), using the following rating scale: o Excellent: 1 dose of factor X was required; or 2 doses of factor X were required less than 48 h apart o Good: 3 doses of factor X were required, with less than 48 h between the first and last dose o Poor: More than 3 doses of factor X were required within any timeframe; or factor X did not work at all o Unassessable: Person did not take any factor X for this bleed; or prior to taking factor X for this bleed, the patient had taken a dose of fresh-frozen plasma, prothrombin complex concentrate or factor IX/X concentrate • Subjects assessment of efficacy (menorrhagic bleeds), , using the following rating scale: o Excellent: 1 dose of factor X was required; or 2 doses of factor X were required less than 48 h apart o Good: 2 doses of factor X were required, with more than 48 h between the first and the last dose o Poor: More than 2 doses of factor X were required; or bleeding could not be kept at a manageable level o Unassessable: Person did not take any factor X for this bleed; or prior to taking factor X for this bleed, the patient had taken a dose of fresh-frozen plasma, prothrombin complex concentrate or factor IX/X concentrate • Investigator's assessment of efficacy (bleeds requiring assessment at the hospital) as 'excellent', 'good', 'poor' or 'unassessable'.

	• Investigator's overall assessment of efficacy as 'excellent', 'good', 'poor' or 'unassessable'; • Total dose of factor X (IU and IU/kg FX:C), total number of infusions and average dose per infusion to treat a new bleed and ongoing bleeds, for any additional preventative use and overall use per subject; • Total dose of factor X (IU/kg FX:C) to treat a bleed (including initial dose for new bleeds and any repeated doses for ongoing bleeds), number of infusions and dose per infusion on a per bleed and a per subject basis; • Dose of factor X per infusion for all infusions, all infusions to treat bleeds, all first infusions to treat bleeds, all subsequent infusions to treat bleeds and all infusions given as a preventative measure. • Average monthly and yearly dose of factor X (IU/kg FX:C) and average monthly and yearly number of infusions to treat a bleed, for any additional preventative use and overall use per subject • Number of exposure days overall and per subject; • Average number of bleeds per subject per month; • Number of bleeds including severity, duration, location and cause
	Safety outcomes: • Adverse events
Source of funding	Bio Products Laboratory Ltd (Elstree, UK)
Abbreviations	FX, factor X; FX:C, factor X functional activity; IU, international units

Modified NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	1/2	Research aim clearly stated. Although the design of the study is reported, the authors do not report key elements of the methodology, for example, the primary outcomes of the study are not explicitly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The open-label, non-randomised, unblinded design of the study was considered adequate by the regulators in light of the orphan setting and the given design and objectives of the trial, where it is evident

		that feasibility issues drive the number of patients enrolled (EPAR:Coagadex). However, the study design is itself limited for determining the benefits of an intervention.
3. Are the methods clearly described? Are the methods appropriate?	1/2	Certain parts of the methodology not fully reported in the publication, for example the number of centres and how participants were selected.
4. Are the data adequate to support the authors' interpretations/ conclusions? Have issues of bias, confounding and study power been considered and addressed?	1/2	The authors conclude that human coagulation factor X is "safe and efficacious for on-demand treatment and short-term prophylaxis in subjects with moderate or severe hereditary FX deficiency". Data partially supports authors' conclusions. The EPAR states that all end points were exploratory and no formal hypothesis testing was planned. No power calculation was performed, the sample size of the study was based on formal scientific advice received from the EMA and FDA.
5. Are the results generalisable to the decision problem?	2/2	Study included people with moderate to severe factor X deficiency (plasma FX:C <5 IU/100 ml).
Total	6/10	
Applicability *	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 5 Ten03 study (Escobar et al. 2016; published paper includes analysis of a subgroup of people in the Ten01 study who underwent surgery)

Study	Escobar MA, Auerswald G, Austin S et al. (2016) Experience of a

reference	new high-purity factor X concentrate in subjects with hereditary factor X deficiency undergoing surgery. Haemophilia, 22(5): 713–20
Unique identifier	NCT01086852
Study type	Analysis of participants from 2 open-label, non-randomised studies (Ten01 and Ten03) who underwent surgery. P1 Primary research using quantitative approaches
Aim of the study	To evaluate the efficacy and safety of plasma-derived factor X concentration for people aged 12 years and over with mild to severe hereditary factor X deficiency undergoing surgery
Study dates	March 2011 to January 2014
Setting	7 centres in the US, Spain, Turkey and the UK
Number of participants	Ten03: 2 participants who underwent 2 procedures each Analysis in Escobar et al. (2016) included 3 participants from the Ten01 study who underwent 1 procedure each
Population	People aged 12 years and over (median age 20 years [range 12 to 58]; 63% female) with mild to severe hereditary FX deficiency (plasma FX:C <20 IU/100 ml)
Inclusion criteria	• People aged 12 years or older with mild to severe hereditary factor X deficiency (plasma FX:C <20 IU/100 ml) • Previously untreated subjects, or those currently treated with fresh frozen plasma (FFP), prothrombin complex concentrate (PCC) or factor IX/X concentrate by prophylaxis or on demand. • History of unusual bleeding, either spontaneously or after surgery or trauma, in the absence of treatment with a factor X containing product. • Pregnant subjects undergoing obstetric delivery (including Caesarean surgery and vaginal delivery) were eligible for inclusion, although none were included.
Exclusion criteria	• History of factor X inhibitor development, or positive for factor X inhibitors at screening • People who were thrombocytopaenic • Clinically significant renal or liver disease • Presences of another coagulopathy or known thrombophilia
Intervention(s)	Human coagulation factor X Dose was intended to raise plasma FX:C levels to 70–90 IU/100ml between 1 and 4 hours before surgery. The maximum permitted individual dose was 60 IU/kg
Comparator(s)	None (single-arm study)
Length of follow-up	Up to 24 months
Outcomes	Primary outcomes: • Clinical estimation of volume of blood loss during surgery • Clinical estimation of volume of blood loss during surgery compared with people without a bleeding disorder

	• Number of post-operative bleeding episodes • Change of haemoglobin from pre-surgery till end of treatment • Number of participants with degree of bleeding control rated as excellent by investigator. The following definitions were used to assess control of bleeding during and after surgery: o Excellent: Parameters are similar to those in subjects without a bleeding disorder o Good: Parameters are inferior to those in subjects without a bleeding disorder, but no other factor X-containing agents were required to restore haemostasis o Poor: Blood loss was excessive (defined as more than twice the predefined amount that would be expected in a subject without a bleeding disorder for this type of surgery); or Haemostasis was not achieved; or Additional factor X-containing agents were required to restore haemostasis o Unassessable: Efficacy was not possible to assess, or Additional factor X-containing agents (excluding blood transfusions) were required before factor X efficacy could be assessed
	Secondary outcomes: • Factor X functional activity (FX:C) incremental recovery (IR) 30 minutes after bolus dose • Dose per infusion (IU/kg)
	Safety outcomes: • Adverse events reported
Source of funding	Bio Products Laboratory Ltd (Elstree, UK)
Abbreviations	FX:C, factor X functional activity; IU, International Units;

Modified NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	1/2	Research aim clearly stated. Although the design of the study is reported, the authors do not report key elements of the methodology, for example, the primary outcomes of the study are not explicitly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The open-label, non-randomised, unblinded design of the study is acceptable given the rarity of the condition and orphan nature of the treatment.

		However, the study design is itself limited for determining the benefits of an intervention.
3. Are the methods clearly described? Are the methods appropriate?	1/2	Certain parts of the methodology not fully reported in the publication, for example the number of centres and how participants were selected.
4. Are the data adequate to support the authors' interpretations/conclusions? Have issues of bias, confounding and study power been considered and addressed?	1/2	The authors conclude that human coagulation factor X is "safe and effective as replacement therapy in five subjects with mild-to-severe FX deficiency undergoing surgery on seven occasions". Data partially supports authors' conclusions. All end points were exploratory and no formal hypothesis testing was planning. No power calculation was performed.
5. Are the results generalisable to the decision problem?	1/2	The study included people with mild factor X deficiency who were undergoing major surgery, and people with severe deficiency undergoing minor surgery. However, there were no people with severe deficiency undergoing major surgery, and no children aged less than 12 years, limiting generalisability.
Total	5/10	
Applicability *	Directly applicable	The intervention and indication are directly relevant to the decision problem

Table 6 Ten02 study (Liesner et al. 2018)

Study reference	Liesner R, Akanezi C, Norton M et al. (2018) Prophylactic treatment of bleeding episodes in children <12 years with moderate to severe hereditary factor X deficiency (FXD): Efficacy and safety of a high-purity plasma-derived factor X (pdFX) concentrate. Haemophilia. Published first online 10.1111/hae.13500

Unique identifier	NCT01721681
Study type	Open label, non-randomised phase 3 study (P1 Primary research using quantitative approaches)
Aim of the study	To evaluate the efficacy, safety and pharmacokinetics of human coagulation factor X for the prophylaxis of bleeding in people aged less than 12 years with moderate or severe hereditary factor X deficiency.
Study dates	April 2015 to October 2016
Setting	3 specialist centres in the UK (Addenbrookes Hospital, Great Ormond Street Hospital and Sheffield Children's Hospital)
Number of participants	9 participants enrolled and completed 11 treatment cycles
Population	Children aged less than 12 years (56% female) with moderate or severe hereditary factor X deficiency (basal plasma factor X activity <5 IU/dL).
Inclusion criteria	Basal plasma factor X activity <5 IU/100 ml History of severe bleeding or an F10 gene mutation known to cause a severe bleeding phenotype
Exclusion criteria	History of factor X inhibitor development History of thrombocytopaenia Clinically significant renal or liver disease
Intervention(s)	Human coagulation factor X
Comparator(s)	None (single-arm study)
Length of follow-up	6 months (26 weeks)
Outcomes	Primary efficacy outcome: • Efficacy of prophylactic human coagulation factor X treatment in reducing or preventing bleeding over 26 weeks (6 months), as assessed by the investigator at the end-of-study visit. The following efficacy ratings were used (taking into account the participant's risk of breakthrough bleeding [low or high risk], protocol compliance, and attainment of trough FX:C levels ≥5 IU/dL): o Excellent: No minor or major bleeds occurred during the study period, OR lower frequency of bleeds than expected given subject's medical or treatment history o Good: Frequency of bleeds as expected given subject's medical or treatment history o Poor: Higher frequency of bleeds than expected given subject's medical or treatment history, OR human coagulation factor X did not work at all o Unassessable: Subject did not complete 6 weeks of treatment with human coagulation factor X, OR subject developed inhibitors to human coagulation factor X, OR

	failure to meet the minimum trough level due to non-compliance with the dosing regimen
	Secondary efficacy outcomes: • Number of bleeds per month (with a description of severity, duration, location, and cause) • Total dose of human coagulation factor X and number of infusions • Mean human coagulation factor X dose per subject • Mean monthly dose • Number of infusions per participant • Pharmacokinetic assessments of FX:C postdose incremental recovery at baseline and end of study (visits 1 and 5, respectively) Trough FX:C levels at all scheduled and unscheduled study visits
	Safety outcomes: • Adverse events • Assessments of haematology, serum biochemistry, viral serology, FX inhibitor screen and Nijmegen-Bethesda assay, • Vital signs, physical examination, infusion site observations Number of exposure days. A follow-up visit or telephone interview was conducted 28 days after the final study visit to check for any new serious AEs.
Source of funding	Bio Products Laboratory Ltd (Elstree, UK)
Abbreviations	FX, factor X; FX:C, factor X functional activity; IU, international units

Modified NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	2/2	Research aim clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The open-label, non-randomised, unblinded design of the study is acceptable given the rarity of the condition and orphan nature of the treatment. However, the study design is itself limited for determining the benefits of an intervention.
3. Are the methods clearly described? Are the methods appropriate?	1/2	Certain parts of the methodology not fully reported in the publication, for example, how the investigators and

		subjects assessed the effectiveness of the treated bleeds is not reported in the paper.
4. Are the data adequate to support the authors' interpretations/conclusions? Have issues of bias, confounding and study power been considered and addressed?	1/2	The authors conclude that the results of the study demonstrate the efficacy and safety of human coagulation factor X for treating children <12 years with moderate/severe hereditary factor X deficiency. No power calculation was performed. Of the four bleeds that required factor X treatment during the study, only 2 were assessed for efficacy by the investigators and only 3 were assessed by the subject. 2 out of 9 participants were withdrawn erroneously from the study before completing 26 week treatment. These 2 participants were rescreened and completed a second per-protocol treatment cycle. The results for both treatment cycles were merged for analysis using the intent-to-treat/safety population.
5. Are the results generalisable to the decision problem?	1/2	The study included children aged <12 years with factor X deficiency, the majority of whom had severe deficiency. No surgical procedures took place during the study, meaning the effectiveness of human coagulation factor X for the perioperative management of bleeding is unknown.
Total	6/10	
Applicability *	Directly applicable	The intervention and indication are directly relevant to the decision problem

Scoring notes

1. Are the research questions/aims and design clearly stated?	Score 2 points if the research aims and design are both clearly described Score 1 point if the either the research aim or research design is clearly described Score 0 points if neither are clearly described
2. Is the research design appropriate for the aims and objectives of the research?	Score 2 points if the research design (e.g. RCT, cohort, before and after) is appropriate to the objectives Score 1 point if the research design is not clearly described but it can be inferred and appears appropriate, or if it is partially appropriate Score 0 points if it is not appropriate
3. Are the methods clearly described? Are the methods appropriate?	Score 2 points if the methods are described and appropriate. Consider randomisation methods, blinding methods, the methods for handling bias and confounding, and the methods for calculating sample size, where appropriate Score 1 point if the methods are not clearly described but they can be inferred and appear appropriate, or if they are partially appropriate Score 0 points if they are not appropriate
4. Are the data adequate to support the authors' interpretations / conclusions? Have issues of bias, confounding and study power been considered and addressed?	Score 2 points if the data supports the conclusions and issues of bias, confounding and study power have been sufficiently accounted for (either in study methods or analysis) Score 1 point if the data partially supports the conclusions Score 0 points if the data do not support conclusions
5. Are the results generalisable to the decision problem?	Score 2 points if the study results are fully generalisable to the decision problem – consider whether the study PICO match the decision problem PICO Score 1 point if the study results are partially generalisable Score 0 points if the results are not generalisable

Appendix 4 Results tables

Table 7 Austin et al. 2016 (Ten01 study)

	Human coagulation factor X (Coagadex)	Analysis
n	**16**	
Primary outcomes – Pharmacokinetic parameters, measured at baseline and follow-up, total 31 measures		
Mean incremental recovery (IR, adjusted for dosing)	2.00 IU/100 ml per IU/kg	
Median incremental recovery (IR, adjusted for dosing)	2.12 IU/100 ml per IU/kg (IQR 1.79 to 2.37)	
Mean half-life	29.4 hours	
Median half-life (IQR)	28.6 hours (25.75 to 33.10)	
Secondary outcomes – Management of bleeding		
Subject's assessment of efficacy (all bleeds)	187 bleeds included in analysis. Excellent= 170 (90.9%) Good= 14 (7.5%) Poor= 2 (1.1%) Unassessable= 1 (0.5%)	'Treatment success' was defined as all bleeds with a treatment response of Excellent or Good. In total 184 bleeds (98.4%) were treatment successes.
Investigator assessment of efficacy (all bleeds)	42 bleeds included in analysis. Excellent= 37 (88.1%) Good= 4 (9.5%) Poor= 1 (2.4%) Unassessable= 0 (0%)	'Treatment success' was defined as all bleeds with a treatment response of Excellent or Good. In total 41 bleeds (97.6%) were treatment successes.
Number of factor X infusions required to treat a single bleed	One= 155 bleeds (82.9%) Two= 28 bleeds (15.0%) Three= 3 bleeds (1.6%) Four= 1 bleed (0.5%)	Mean number of infusions required to treat a bleed= 1.2 (SD 0.47)
Mean dose per infusion (SD)	25.3 IU/kg (2.4)	The mean cumulative dose of factor X over the study period was 734 IU/kg per participant
Secondary outcome – Prevention of bleeding		
Total number of prophylactic infusions	184 infusions given to 9 participants	Equates to a mean number of infusions

		per person of 20.4, or a mean of 1.62 infusions per person per month.
Mean dose per prophylactic infusion	25.24 IU/kg	
Reasons for prophylactic treatment	Secondary prophylaxis to prevent re-bleeding= 56/184 (30.4%) Short-term prophylaxis= 45/184 (24.5%) Routine prophylaxis= 57/184 (31.0%) Other prophylaxis= 26/184 (14.0%)	The use of human coagulation factor X for routine prophylaxis was a deviation from the treatment regimen prescribed in the protocol
Safety and tolerability outcomes		
n	**16**	
All adverse events (AEs)	176 events (occurring in 16 participants)	The most common AE was headache, with 14 instances in 8 participants (8% of all AEs). All headaches were classed as mild and not related to treatment.
AEs considered possibly related to factor X treatment	6 events (3.4% of all AEs, occurring in 2 participants)	Specific AEs were: fatigue (x2), infusion-site erythema (x2), back pain, pre-dose infusion-site pain.
Abbreviations: IQR, interquartile range; SD, standard deviation		

Table 5 Escobar et al. 2016 (analysis of Ten03 and participants in the Ten01 study who underwent surgery)

	Human coagulation factor X (Coagadex)	**Analysis**
n	**5 participants (7 surgical procedures in total)**	
Primary outcomes (reported separately for each procedure)		
Left knee replacement	Expected blood loss= 150 ml Actual blood loss=150 ml Investigator efficacy assessment=	

	Excellent DRC efficacy assessment= Excellent	
Right knee replacement	Expected blood loss= 50 ml Actual blood loss= 50 ml Investigator efficacy assessment= Excellent DRC efficacy assessment= Excellent	
Coronary artery bypass graft	Expected blood loss= 750 ml Actual blood loss= 402 ml Investigator efficacy assessment= Excellent DRC efficacy assessment= Excellent	
Tooth extraction (x6)	Expected blood loss= 40 ml Actual blood loss= 40 ml Investigator efficacy assessment= Excellent DRC efficacy assessment= Excellent	
Tooth extraction (x1)	Expected blood loss= 10 ml Actual blood loss= 10 ml Investigator efficacy assessment= Excellent DRC efficacy assessment= Excellent	
Tooth extraction (x1)	Expected blood loss= 10 ml Actual blood loss= 10 ml Investigator efficacy assessment= Excellent DRC efficacy assessment= Excellent	
Tooth extraction (x2)[a]	Expected blood loss= 300 ml[b] Actual blood loss= 100 ml[b] Investigator efficacy assessment= Excellent DRC efficacy assessment= Excellent	
Secondary outcomes		
Median factor X functional activity (FX:C) incremental recovery (IR) for pre-surgical infusion	2.21 IU/100 ml per IU/kg (range 1.67 to 2.34)	
Median pre-surgical dose	48.85 IU/kg (range 30.88 to 54.41)	
Safety and tolerability outcomes		
n	**5 (7 procedures)**	
Adverse events occurring during	Total= 31 events Constipation= 3 (10%)	None of the AEs were considered related to

the peri-surgical period	Dyspepsia= 3 (10%) Nausea= 2 (7%) Peripheral oedema= 2 (7%) Post-procedural pain= 2 (7%) Post-procedural discomfort= 2 (7%)	the study drug
Abbreviations: DRC, data review committee; IU, international units		
Notes: [a] This procedure was excluded from the efficacy analysis due to plasma FX:C being >20 IU/100 ml prior to the presurgical dose. [b] Because the teeth for extraction had infected roots and had to be removed from the bone, blood loss for this procedure was expected to be higher than for a routine tooth extraction procedure.		

Table 6 Liesner et al. 2018 (Ten02 study)

	Human coagulation factor X (Coagadex)	**Analysis**
n	**9**	
Primary outcome		
Investigator assessment of prophylactic efficacy over 26 weeks	In the per-protocol population, investigators rated prophylactic efficacy as 'excellent' for all participants.	
Secondary outcomes		
Bleeding (during 26 week period)	A total of 10 bleeds (6 minor, 3 major, and 1 without severity recorded) were reported in 3/9 participants (33%).	
Mean number of prophylactic infusions per participant (SD)	59.7 infusions (5.1)	
Mean dose per participant per infusion	38.8 IU/kg given every 3.1 days (mean 9.3 infusions per month)	
Mean trough FX:C	Screening: 7.9 IU/dL End-of-study: 11.1 IU/dL	
Safety and tolerability outcomes		
n	**16**	
Adverse events (AEs)	28 AEs reported in 8/9 participants (88.9%)	None of the AEs were considered by the investigators to be related to human coagulation factor X treatment.

Serious AEs	2 serious AEs (lower respiratory tract infection and influenza) reported in 1/9 participants (11.1%), hospitalisation required.	Neither serious AE were considered by the investigators to be related to human coagulation factor X treatment.
Abbreviations: dL, decilitre; FX:C, factor X functional activity; IU, international units; SD, standard deviation		

Appendix 5 Grading of the evidence base

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

NSF-LTC scoring notes

2. Are the research questions/aims and design clearly stated?	Yes = 2 In part = 1 No = 0
2. Is the research design appropriate for the aims and objectives of the research?	Yes = 2 In part = 1 No = 0
3. Are the methods clearly described?	Yes = 2 In part = 1 No = 0
4. Are the data adequate to support the authors' interpretations / conclusions?	Yes = 2 In part = 1 No = 0
5. Are the results generalisable?	Yes = 2 In part = 1 No = 0

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	**Criteria**
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable

Grade B	1 study of at least 7/10 which is directly applicable OR More than 1 study of at least 7/10 which is indirectly applicable OR More than 1 study 4-6/10 and at least 1 is directly applicable OR 1 study 4-6/10 which is directly applicable and 1 study of least 7/10 which is indirectly applicable
Grade C	1 study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than 1 study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics

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