

# **Clinical Commissioning Policy: Human coagulation factor X for hereditary factor X deficiency (all ages)**

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# **Clinical Commissioning Policy: Human coagulation factor X for hereditary factor X deficiency (all ages)**

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## Policy Statement

NHS England will not routinely commission human coagulation factor X for people of all ages with hereditary factor X deficiency who need long term prophylaxis in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

## Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

## Plain Language Summary

See also, Section 4 for additional definitions of terms used in this document.

### **About hereditary factor X (ten) deficiency**

Hereditary factor X deficiency is an inherited bleeding disorder caused by a lack of a protein called factor X, which is needed for blood to clot properly and therefore to prevent bleeding. It is passed on when both parents of an individual have a defective copy of the factor X gene, and therefore affects both sexes equally. Hereditary factor X deficiency varies in severity depending on the levels of factor X in the blood. Milder forms of the disease typically present as nosebleeds, easy bruising, prolonged

menstrual bleeding, musculoskeletal bleeds, excessive bleeding following surgery, and bleeding of the gums. The most severe forms of the condition can result in bleeding in the brain or gastrointestinal tract, which can be life-threatening.

Diagnosis of the condition can occur at any age, although more severe forms are often diagnosed within the first month of life. Hereditary factor X deficiency requires life-long treatment which includes preventing or stopping bleeding events. In the UK, it is estimated to affect 1 person in 1,000,000.

### **About current treatments**

Treatments for hereditary factor X deficiency often involve the replacement of factor X. Currently, this is done using a treatment called prothrombin complex concentrate (PCC) which contains factor X as well as additional blood clotting factors that patients with factor X deficiency are not deficient in, including factor II (two), VII (seven), and IX (nine). Also, less commonly fresh frozen plasma (a blood product made from the liquid portion of whole blood) is used, however, this also contains other proteins and clotting factors apart from factor X.

### **About the new treatment**

Human coagulation factor X is a concentrate of the protein called factor X derived from human plasma (the colourless liquid part of blood). It has a marketing authorisation in the UK for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency. It is one of the proteins which is needed for blood to clot. Human coagulation factor X temporarily replaces the missing factor X in people with hereditary factor X deficiency. It is used to prevent bleeding in patients with hereditary factor X deficiency, including during surgery.

### **What we have decided**

NHS England has carefully reviewed the evidence to treat people of all ages with hereditary factor X deficiency who need long term prophylaxis with human coagulation factor X. NHS England recognises that the published evidence identifies that, at present, there is sufficient evidence to commission this treatment. However, following the relative prioritisation process undertaken in November 2018 for funding

interventions in 2019/20, NHS England has concluded that, balanced against other relative priorities that were also considered during this process, human coagulation factor X to treat people of all ages with hereditary factor X deficiency, will not be funded at this time within the resources available.

## 1 Introduction

Hereditary factor X deficiency is an inherited bleeding disorder caused by a lack of a protein called factor X, which is needed for blood to clot properly. It is passed on when both parents of an individual have a defective copy of the factor X gene, and therefore affects men and women equally. Hereditary factor X deficiency varies in severity depending on the levels of factor X in the blood. Milder forms of the disease typically present as nosebleeds, easy bruising, prolonged menstrual bleeding, musculoskeletal bleeds, excessive bleeding following surgery, and bleeding of the gums. The most severe forms of the condition can result in bleeding in the brain or gastrointestinal tract, which can be life-threatening. Diagnosis of the condition can occur at any age, although more severe forms are often diagnosed within the first month of life. Hereditary factor X deficiency requires life-long treatment which includes preventing or stopping bleeding events. In the UK, it is estimated to affect 1 person in 1,000,000 ([Austin et al. 2016](#)).

Human coagulation factor X is a concentrate of the protein called factor X derived from human plasma (the colourless liquid part of blood). It has a marketing authorisation in the UK for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency. It is one of the proteins which is needed for blood to clot. Human coagulation factor X temporarily replaces the missing factor X in people with hereditary factor X deficiency.

It is licensed by the European Medicines Agency '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](#)). It is administered intravenously. Dosage depends on body surface area and age.

Human coagulation factor X is expected to be used in people of all ages to prevent bleeding events.

Treatment may last for many years, since human coagulation factor X is not curative. The Summary of Product Characteristics for human coagulation factor X states that 'treatment should be initiated under the supervision of a physician experienced in the treatment of rare bleeding disorders'.

## 2 Definitions

- Central venous access device (CVAD) – a tube that is inserted into and positioned within a vein in the body to allow treatments to be delivered into the bloodstream.
- Coagulation factor proteins – a set of proteins, including factor X, which are involved in helping the blood to clot.
- Factor X – one of several ‘coagulation factor proteins’ needed for blood to clot properly.
- Pro-thrombin complex (PCC) – a treatment for bleeding in people with certain clotting factor deficiencies. It contains factor X as well as additional factors that patients with factor X deficiency are not deficient in, including factor II (two), VII (seven), and IX (nine).
- Haemophilia – an inherited bleeding disorder resulting from a deficiency in clotting factor VIII or IX that means the person’s body is unable to make blood clots which are needed to stop bleeding. This results in spontaneous bleeding or bleeding after an injury or surgery with a pattern of bleeding that differs from hereditary factor X deficiency.
- Plasma - the colourless liquid part of blood which remains after the blood cells have been removed.
- Hereditary factor X deficiency - a genetic condition caused by not having enough of the protein known as factor X in your blood.
- Thrombosis - formation of a blood clot inside a blood vessel. This blockage in the blood vessel can lead to tissue damage in the area. A piece of the blood clot can also break off and lodge itself elsewhere in the body causing further complications.

## 3 Aims and Objectives

This policy considered human factor X concentrate to prevent bleeding in patients of all ages with hereditary factor X deficiency.

The objectives were to:

- ensure evidence based commissioning with the aim of improving clinical outcomes for patients of all ages with hereditary factor X deficiency; and
- identify clinical criteria for preventing bleeds in patients with hereditary factor X deficiency.

## 4 Epidemiology and Needs Assessment

### Epidemiology

Hereditary factor X deficiency requires life-long treatment which includes preventing or stopping bleeding events. In the UK, it is estimated to affect 1 person in 1,000,000 ([Austin et al. 2016](#)). Based on the UK Haemophilia database, there are approximately 35 people with hereditary factor X deficiency in the UK who receive treatment in a year.

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). Severe factor X deficiency cases are readily apparent at birth as the level of factor X is extremely low (less than 1 IU/dL of blood). In moderate cases, 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).

See table below:

Estimates	Data source	Number of people
Population in England in mid-2016	<a href="#">Office for National Statistics</a>	55,268,100
Between 1 and 4 people in 1,000,000 with Hereditary factor X deficiency	<a href="#">Austin et al. 2016</a> and <a href="#">UK Haemophilia database (http://www.ukhcdo.org/wp-content/uploads/2017/07/Bleeding_Disorder_Statistics_for_April_2015_-_March_016-forUKHCDO_Wbsite_V2.pdf)</a>	55 – 241
People with hereditary factor X deficiency who require medical treatment in a year	<a href="#">UK Haemophilia database Statistics_for_April_2015_-_March_016-forUKHCDO_Wbsite_V2.pdf)</a>	35

### Needs assessment

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. Both PCCs available have marketing authorisations 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’. 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 and relatively small amounts of factor X, the volumes of PCC needed to achieve haemostasis (normal levels of blood clotting) are large and can be too large for infants and children with factor X deficiency. 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. Treatment with smaller volumes than the use of concentrated factor X allows could result in reduced hospital visits. Moreover, infants and children with severe hereditary factor X deficiency often require a central venous access device (CVAD) 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 PCC 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).

## 5 Evidence Base

NHS England has considered evidence from the clinical evidence review that supports the development of this policy.

### Treatment of bleeds

[Austin et al. 2016](#) (Ten01) was an open-label, non-randomised study including 16 people with moderate or severe hereditary factor X deficiency. At baseline 2 out of 16 participants were classified as having moderate factor X deficiency (defined as a factor X concentration of 1 to 5 IU/100 ml in their blood) and 14 out of 16 participants as having severe factor X deficiency (defined as a factor X concentration of less than 1 IU/100 ml in their blood). The study reported that nearly all bleeding events treated with human coagulation factor X were considered 'treatment successes'. The study used two methods for assessing treatment success: subject assessment and investigator assessment. Of the 187 analysed bleeding events, the subjects assessed their response to treatment as 'excellent' for 170 bleeds (90.9%) and 'good' for 14 bleeds (7.5%). Two bleeding events (1.1%) were assessed as a 'poor' response and considered treatment failures, and one bleeding event was not assessable. The investigators assessed response to treatment in 42 bleeding events in 10 out of 16 participants. In total, 37 bleeding events (88.1%) were assessed as having an 'excellent' response to treatment and

four bleeding events (9.5%) a good response. One bleeding event (2.4%) had a 'poor' response and was reported as a 'treatment failure'.

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 were controlled for ethical reasons. The numbers of patients with hereditary factor X deficiency included in the studies is small. However, hereditary factor X deficiency is a very rare condition, therefore the potential number of participants for clinical trials is limited, as noted by the regulators in the European Public Assessment Report (EPAR). The EPAR also states that "clinical experience has already been obtained with prothrombin complex concentrates, where factor X is a component together with other plasma derived products. As such by design – enrichment of factor X and depletion of other (coagulation) proteins – an increased safety profile (wa)s expected." Furthermore, the EPAR states that "as the role of human plasma derived factor X in the coagulation cascade is clear, the absence of pharmacodynamic studies (wa)s justified."

### **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 (reported in the [EPAR: Coagadex](#)). 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 EPAR reported that in the 2 participants who received long-term prophylaxis with human coagulation factor X, the mean number of bleeding events reduced from 0.23 and 0.82 bleeding events per month when not on treatment to 0 bleeding events per month when receiving infusions of human coagulation factor X.

## **Perioperative management of bleeding**

Escobar et al 2016 (Ten03) was an open-label, non-randomised study which evaluated the efficacy and safety of human coagulation factor X for the management of bleeding before and after surgery in 2 patients. Each patient had 2 surgical procedures performed. Escobar also reported outcomes for 3 participants from the Ten01 study who underwent 1 surgical procedure each.

For all 7 surgical procedures, the study reported that 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.

## **Safety and tolerability**

Across the 2 open-label, single arm studies (Ten01 and Ten03) no participants developed factor X inhibitors (antibodies to human coagulation factor X) 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 that all headache events were mild and not thought to be related to 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.

Since the approval of human coagulation factor X in the US (Oct 2015) and EU (16 Mar 2016) a total of 3 non-serious spontaneous reports have been reported. There have been no reports of thrombogenicity, inhibitor development or transmission of infectious diseases since the launch of human coagulation factor X. A Periodic Safety Update Report (PSUR) was undertaken for human coagulation factor X between 17 Sept 2016 and 16 Mar 2017 and there were no reports of factor X inhibitors with human coagulation factor X.

## **Studies in children under 12 years**

Liesner et al. 2018 (Ten02) is an open-label, non-randomised study in children aged under 12 years with moderate (n=1) or severe (n = 8) factor X deficiency. The study investigated the efficacy and safety of routine prophylaxis with human coagulation factor X over 6 months. Results were reported for the 9 patients (mean age of 6.8 years). In the 6 month period, 537 prophylactic infusions of human coagulation factor X were administered. During that time 10 bleeding events occurred in 3 of 9 children: 6 minor, 3 major, 1 unassessed. A total of 28 adverse events were reported in 8 children; none were considered to be related to treatment. No evidence of inhibitor development was seen.

A case study by Khair 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). The CVAD, which was the child's fifth, became blocked 2 years after insertion. This meant that 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, 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 with no CVAD blockages.

## **Long-term prophylaxis**

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). The effectiveness of prophylaxis was assessed by the investigators over 26 weeks, after which time treatment for all participants was assessed as 'excellent'.

## **6 Documents Which Have Informed this Policy**

The policy replaces NHS England Clinical Commissioning Policy 170052P Clinical Commissioning Policy: Human Coagulation Factor X for hereditary factor X deficiency (all ages) (published July 2018).

The documents that have informed this policy include a review of the clinical evidence available for human coagulation factor X and a submission from Bio Products Laboratory. Additional evidence sources are listed in the table of references below.

## **7 Date of Review**

This document will be reviewed when information is received which indicates that the policy requires revision.

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