ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Coagadex 250 IU powder and solvent for solution for injection
Coagadex 500 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Coagadex 250 IU powder and solvent for solution for injection
Each vial contains nominally 250 IU human coagulation factor X.
Coagadex contains approximately 100 IU/mL human coagulation factor X after reconstitution with 2.5 mL sterilised water for injections.

Coagadex 500 IU powder and solvent for solution for injection
Each vial contains nominally 500 IU human coagulation factor X.
Coagadex contains approximately 100 IU/mL human coagulation factor X after reconstitution with 5 mL sterilised water for injections.

Produced from the plasma of human donors.

Excipients with known effect:
Coagadex contains up to 0.4 mmol/mL (9.2 mg/mL) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder vial containing white or off-white powder.

Solvent vial containing clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Coagadex is indicated for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency.

Coagadex is indicated in all age groups

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of rare bleeding disorders.

Posology
The dose and duration of the treatment depend on the severity of the factor X deficiency (i.e. the patient's baseline factor X level), 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 in any age group.

In adults and adolescents at least 12 years of age, the expected *in vivo* peak increase in factor X level expressed as IU/dL (or % of normal) can be estimated using the following formulae:

Dose (IU) = body weight (kg) x desired factor X rise (IU/dL or % of normal) x 0.5

OR

Increase in factor X level (IU/dL or % of normal) = [total dose (IU)/body weight (kg)] x 2

The following examples assume the patient's baseline factor X level is <1 IU/dL:

1. A dose of 2000 IU Coagadex administered to a 70 kg patient should be expected to result in a peak post-infusion factor X increase of 2000 x {[2 IU/dL]/[IU/kg]}/[70 kg] = 57 IU/dL (i.e. 57% of normal)
2. A peak factor X level of 90% of normal is required in a 70 kg patient. In this situation, the appropriate dose would be:

   70 kg x 90 IU/dL/{[2 IU/dL]/[IU/kg]} = 3150 IU.

The dose and frequency should be based on the individual clinical response. Patients may vary in their pharmacokinetic (e.g. half-life, *in vivo* recovery) and clinical responses to Coagadex. Although the dose can be estimated using the calculations above, whenever possible appropriate laboratory tests, such as serial factor X assays, should be performed to guide dose adjustments.

Control of bleeding episodes
Adults and adolescents aged 12 years or more for treatment of bleeding episodes: 25 IU/kg Coagadex should be injected when the first sign of bleeding occurs or just before the expected onset of menstrual bleeding. Repeat 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 Coagadex should be injected and repeated as required.

Routine prophylaxis of bleeding episodes
Due to inter-and intra-patient variability, it is recommended that trough blood levels of Factor X should be monitored at intervals, especially in the first weeks of therapy or after dose changes. Dose regimen should be adjusted to clinical response and trough levels of Factor X of at least 5 IU/dL.

There are limited data on the use of Coagadex for long periods of prophylaxis in adults. There are no data available on routine prophylaxis in paediatric patients aged >12 to <18 years. 25 IU/kg twice weekly is the proposed starting dose for prophylaxis in patients >12 years of age with dose levels and dosing intervals to be adjusted as clinically indicated. Depending on individual clinical response, longer intervals, e.g. once weekly, might be adequate (see section 5.1).

Perioperative Management (Adults and adolescents aged at least 12 years of age)
Pre-surgery**:** calculate dose of Coagadex to raise plasma factor X levels to 70-90 IU/dL. The careful control of dose and duration of treatment is especially important in cases of major surgery.

Required dose (IU) = body weight (kg) x desired factor X rise (IU/dL) x 0.5

The desired factor X rise is the difference between the patient's plasma factor X level and the desired level, and based on the observed recovery of 2 IU/dL per IU/kg.

Example: to raise plasma factor X level from 15 IU/dL to 90 IU/dL in a 70 kg patient, the appropriate dose is:

70 x (90-15) x 0.5 = 2,625 IU.

Post-surgery: dose as necessary to maintain plasma factor X levels at a minimum of 50 IU/dL until the subject is no longer at risk of bleeding due to surgery.

It is recommended that post-infusion plasma factor X levels are measured for each patient before and after surgery, to ensure that haemostatic levels are obtained and maintained.

Elderly
No dose adjustment is necessary.

Renal impairment
No dose adjustment is necessary.

Hepatic impairment
No dose adjustment is necessary.

Paediatric population
For on-demand control of bleeding in children aged less than 12 years: 30 IU/kg Coagadex should be injected when the first sign of bleeding occurs. Repeat 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: 30 IU/kg Coagadex should be injected and repeated as required.

For routine prophylaxis of bleeding episodes in children aged less than 12 years: 40 IU/kg twice weekly. Due to inter-and intra-patient variability, it is recommended that trough blood levels of Factor X should be monitored at intervals, especially in the first weeks of therapy or after dose changes. Dose regimen should be adjusted to clinical response and trough levels of Factor X of at least 5 IU/dL. Some patients may achieve desired FX trough levels on once weekly prophylactic therapy (see section 5.1).

For perioperative management in children aged less than 12 years: Pre-surgery**:** calculate dose of Coagadex to raise plasma factor X levels to 70-90 IU/dL. The careful control of dose and duration of treatment is especially important in cases of major surgery.

The expected *in vivo* peak increase in factor X level expressed as IU/dL (or % of normal) can be estimated using the following formulae:

Dose (IU) = body weight (kg) x desired factor X rise (IU/dL or % of normal) x 0.6

OR

Increase in factor X level (IU/dL or % of normal) = [total dose (IU)/body weight (kg)] x 1.7

Post-surgery: dose as necessary to maintain plasma factor X levels at a minimum of 50 IU/dL until the subject is no longer at risk of bleeding due to surgery.

It is recommended that post-infusion plasma factor X levels are measured for each patient before and after surgery, to ensure that haemostatic levels are obtained and maintained.

Method of administration
Intravenous use.

After reconstitution, the product should be administered intravenously at a suggested rate of 10 mL/min, but no more than 20 mL/min.

For home therapy, the patient should be given appropriate training and reviewed at intervals.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity
Allergic type hypersensitivity reactions, including anaphylaxis, are possible. Coagadex contains traces of human proteins other than factor X. Patients should be informed of the early signs of hypersensitivity reactions including angioedema, infusion site inflammation (e.g. burning, stinging, erythema), chills, cough, dizziness, fever, flushing, generalised urticaria, headache, hives, hypotension, lethargy, musculoskeletal pains, nausea, pruritus, rash, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing. If any of these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician. In case of shock, the current medical standards for shock treatment should be observed.

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor X is a possible complication in the management of individuals with factor X deficiency.

In general, all patients treated with human coagulation factor X should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If expected factor X activity levels are not attained, or if bleeding is not controlled with an expected dose, perform an assay that measures factor X inhibitor concentration.

Factor Xa inhibitors
Coagadex is likely to be counteracted by factor Xa inhibitors, direct or indirect. These antithrombotic agents should not be used in patients with factor X deficiency. Coagadex should not be used as an antidote to the effects of direct oral anti-coagulants (DOACs) in patients who do not have factor X deficiency.

Transmissible agents
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

Vaccination against hepatitis A and B in patients who regularly or repeatedly receive human plasma-derived Factor X products may be warranted.

Sodium content
Coagadex contains up to 9.2 mg sodium per mL of reconstituted solution, equivalent to 0.0046% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Coagadex is likely to be counteracted by factor Xa inhibitors, direct or indirect (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Due to the rarity of hereditary factor X deficiency, experience regarding the use of Coagadex during pregnancy and breast-feeding is not available. Therefore, Coagadex should be used during pregnancy only if clearly indicated.

Breast-feeding
Due to the rarity of hereditary factor X deficiency, experience regarding the use of Coagadex during pregnancy and breast-feeding is not available. Therefore, Coagadex should be used during breast-feeding only if clearly indicated.

Fertility
Animal reproduction studies have not been conducted with Coagadex.

4.7 Effects on ability to drive and use machines

Coagadex has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The adverse reactions (ADRs) that occurred in the highest frequency were infusion site erythema, infusion site pain, fatigue, and back pain.

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely with treatment of other haemophilias and may in some cases have progressed to severe anaphylaxis (including shock). Hypersensitivity reactions, allergic reactions, and anaphylaxis have not been reported in Coagadex clinical trials.

Tabulated list of adverse reactions

The following adverse reactions have been reported in clinical studies involving 27 patients treated with Coagadex. Frequencies have been evaluated according to the following convention: very common (≥1/10 subjects); common (≥1/100 to <1/10). Frequencies of uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000) cannot be estimated from the available data.

Tabulated list of adverse reactions

MedDRA System Organ Class	Adverse reaction	Frequency
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Infusion site erythema Infusion site pain Fatigue	Common

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults (see section 5.1).

For safety information with respect to transmissible agents, see section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

One case of accidental overdose was reported in the clinical trials, in which a subject received approximately 80 IU/kg Coagadex to treat a bleed. No adverse events were reported relating to this overdose. However, there is a potential for thromboembolism with overdose which is likely to be associated with a reduced prothrombin time below the normal range. Careful clinical assessment by an experienced clinician is recommended with or without use of the Wells score, clinical laboratory tests of haemostasis and appropriate ultrasound imaging. Treatment of proven or suspected DVT should follow the usual procedures but with monitoring FX.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-haemorrhagics, vitamin K and other haemostatics, coagulation factor X, ATC code: B02BD13.

Mechanism of action
Factor X is an inactive zymogen, which can be activated by factor IXa (via the intrinsic pathway) or by factor VIIa (via the extrinsic pathway). Factor X is converted from its inactive form to the active form (factor Xa) by the cleavage of a 52-residue peptide from the heavy chain. Factor Xa associates with factor Va on a phospholipid surface to form the prothrombinase complex, which activates prothrombin to thrombin in the presence of calcium ions. Thrombin then acts upon soluble fibrinogen and factor XIII to generate a cross-linked fibrin clot.

Pharmacodynamic effects
Coagadex is derived from human plasma and used as a replacement for the naturally existing coagulation factor X in patients with hereditary factor X deficiency.

Clinical efficacy

In a multicentre, open-label, non-randomised clinical trial to evaluate the pharmacokinetics, safety and efficacy of Coagadex, 16 subjects (aged 12 years and above) with moderate to severe hereditary factor X deficiency (FX:C < 5 IU/dL) received a dose of 25 IU/kg Coagadex to treat spontaneous, traumatic and menorrhagic bleeding episodes.

The efficacy of Coagadex in treating bleeding episodes was assessed by the subject and/or investigator for each new bleeding episode, using a pre-determined bleed-specific ordinal rating scale of excellent, good, poor and unassessable. Of the 208 bleeding episodes treated with Coagadex, 187 bleeding episodes in 15 subjects were evaluated for efficacy. Ninety eight (53%) were major bleeding episodes, and 88 (47%) were minor bleeds (one bleed was not assessed). Coagadex was considered to be good (7%) or excellent (91%) in treating 98% of bleeding episodes. Of the 187 bleeding episodes in the efficacy analysis, 155 bleeds (83%) were treated with one infusion, 28 bleeds (15%) with two infusions, 3 bleeds (2%) with three infusions and 1 bleed (0.5%) with four infusions. The mean dose per infusion and total dose of Coagadex were 25.4 IU/kg and 30.4 IU/kg, respectively. Four bleeding episodes in two subjects were considered treatment failures. The recommended dose of 25 IU/kg Coagadex to treat a bleed was maintained during the study for 14 of the 16 subjects. The other two subjects used doses up to 30 IU/kg and 33 IU/kg.

A total of 184 infusions of Coagadex were given as a preventative measure. Routine prophylaxis was used by two subjects. One subject, aged 58 years, used 28 IU/kg once weekly for 8 weeks and, later, 25 IU/kg every 2 weeks for more than 5 months. The other subject, aged 22 years, used 24.6 IU/kg once weekly for 8.5 months. Neither subject had any bleeds during these periods.

Prophylaxis of Bleeding Episodes

The third study evaluated the use of Coagadex in routine prophylaxis of bleeding episodes in nine children aged less than 12 years of age. The mean age was 7.3 (range 2.6 to 11.9) years. Eight subjects had severe FX deficiency, the other had moderate deficiency. Four subjects were aged 0 to 5 years and five were aged 6 to 11 years inclusive. Routine prophylaxis was started with unit doses of 40-50 IU/kg and during the first 6 weeks trough levels of Factor X were measured to adjust the dose regimen to maintain a trough level of at least 5 IU/dL. A total of 537 (mean 59.7 per subject) prophylactic infusions were administered. The median prophylactic dose per infusion per subject was 39.60 IU/kg (mean 38.76 IU/kg), and ranged from 18.0 to 47.3 IU/kg. Median and mean doses per infusion in the four children less than 6 years of age were both 40.1 IU/kg (95% CI 30.70, 49.57) and in the five children 6 to 11 years of age inclusive, median dose was 39.6 IU/kg and mean dose was 37.7 IU/kg (95% CI: 23.42, 51.91). The median dose interval for all of the nine children was 3 days (range 2 to 8 days). Six children (66.7%) remained free of bleeds during routine prophylaxis. Three children (33.3%), one in the 0-5 years age group and two in the 6-11 years age group had a total of 10 bleeds due to epistaxes, trauma or menorrhagia. All were treated with a single infusion of Coagadex; mean and median doses 31.7 IU/kg (range 24.6 to 38.8 IU/kg) and all recorded efficacy ratings were categorized as excellent. There were no adverse drug reactions in this study in children less than 12 years of age.

Surgical haemostasis

The safety and efficacy of Coagadex for perioperative management was evaluated in five subjects aged 14 to 59 years with mild (n=2), moderate (n=1), and severe (n=2) disease, who underwent a total of seven surgical procedures.

For all surgical procedures, Coagadex was assessed as excellent (no post-operative bleeding, no requirement of blood transfusions, and blood loss was no more than 'as expected') in controlling blood loss during and after surgery. For major surgery, a median of 13 infusions (range 2 to 15 infusions) and a median cumulative dose of 181 IU/kg (range 45 to 210 IU/kg) were required to maintain haemostasis. For minor surgery, a median of 2.5 infusions (range 1 to 4 infusions) and a median cumulative dose of 89 IU/kg (range 51 to 127 IU/kg) were used to maintain haemostasis.

5.2 Pharmacokinetic properties

In a clinical study of Coagadex in subjects with severe or moderate factor X deficiency (basal FX:C <5 IU/dL), the pharmacokinetics of Coagadex were assessed in 16 subjects after administration of a nominal dose of 25 IU/kg. Pharmacokinetic (PK) parameters were calculated from plasma factor X:C (one-stage clotting assay) activity measurements after subtraction of the pre-dose value. Combining IR values for FX:C at the baseline visit (n=16) and the Repeat PK assessment (n=15) gave an overall geometric mean IR of 2.07 IU/dL per IU/kg administered (n=31). Similarly, combining $t_{½}$ values at the Baseline Visit and the Repeat PK assessment gave an overall geometric mean $t_{½}$ of 29.36 hours. Systemic exposure to FX:C at the Repeat PK visit (at least 6 months later) was equivalent to that at baseline, since repeat/baseline ratios for all PK parameters were within the range of 90% to 110%.

The mean (CV%) for incremental recovery was 2.08 (18.1). The mean (CV%) maximum plasma concentration (C_{max}) was 0.504 (17.2) IU/mL.
The mean (CV%) for area under the curve (AUC_{0-144h}) was 17.1 (21.0) IU.hr/mL.
Human coagulation factor X is largely retained within the vascular compartment: mean apparent volume of distribution (V_{ss}) was 56.3 (24.0) mL/kg.
The mean (CV%) half-life of human coagulation factor X was 30.3 (22.8) hr and clearance was 1.35 (21.7) mL/kg/hr.

Renal impairment
No pharmacokinetic studies have been conducted but there is no anticipated effect of gender or renal function on the pharmacokinetic profile of Coagadex.

Hepatic impairment
No pharmacokinetic studies have been conducted but there is no anticipated effect of gender or hepatic function on the pharmacokinetic profile of Coagadex.

Elderly
No pharmacokinetic studies have been conducted but there is no anticipated effect of age on the pharmacokinetic profile of Coagadex.

Paediatric population
Pharmacokinetic studies have not been performed in children under the age of 12 years. The study in children (see section 5.1) measured incremental recovery at 30 min (IR_{30min}) after the first dose and after the last dose in the study (approximately 6 months later) (see section 5.1) Combining IR_{30min} values for FX:C at the baseline visit (n=9) and the Repeat PK assessment (n=9) gave an overall geometric mean IR of 1.74 (range 1.3-2.2) IU/dL per IU/kg administered (n=9). For the subgroup aged 6-11 years (n=5), the geometric mean IR_{30min} was 1.91 (range 1.6 -2.2) IU/mL per IU/kg and for the youngest subgroup, 0-5 years (n=4) was 1.53range 1.3-1.8) IU/mL per IU/kg.

Trough levels of FX:C were measured during the first 6 weeks of the study to individualise the dose regimen and to maintain a trough level of at least 5 IU/dL. During the dose-adjustment phase, two trough levels were $\leq$5 IU/dL but thereafter none were below this threshold.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeat-dose toxicity, thrombogenicity and local tolerability.

No investigations on genotoxicity, carcinogenicity and reproductive or developmental toxitcity have been conducted since human plasma coagulation factor X (as contained in Coagadex) is an endogenous protein.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Citric acid
Sodium hydroxide (for pH adjustment)
Disodium phosphate dihydrate
Sodium chloride
Sucrose

Solvent
Water for injections

6.2 Incompatibilities

In the absence of compatability studies, this medicinal product must not be mixed with other medicinal products.

The product should only be reconstituted using the Mix2Vial that is provided in the pack (see section 6.6).

6.3 Shelf life

3 years.

After reconstitution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 1 hour at room temperature (up to 25°C +/-2°C).

6.4 Special precautions for storage

Do not store above 30°C.

Do not freeze.

Keep container in the outer carton in order to protect it from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Immediate containers
Powder vial: 250 IU or 500 IU of human coagulation factor X in a type I glass vial stoppered with a halobutyl rubber stopper, oversealed with a snap-off polypropylene cap and aluminium lacquered skirt.
Solvent vial: 2.5 mL or 5 mL solution in a type I glass vial sealed with a halobutyl rubber stopper and an overseal.
Transfer Device (Mix2Vial).

Pack sizes
Coagadex 250 IU
1 vial 250 IU human coagulation factor X powder for solution for injection
1 vial 2.5 mL water for injections
1 Transfer Device (Mix2Vial)

Coagadex 500 IU
1 vial 500 IU human coagulation factor X powder for solution for injection
1 vial 5 mL water for injections
1 Transfer Device (Mix2Vial)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The powder should only be reconstituted with the water for injections provided in the pack. The 250 IU and 500 IU presentations should be reconstituted using 2.5 mL and 5 mL water for injections, respectively.

Do not use the water for injections if signs of particulate matter are visible.

The vials should be brought to room temperature (not above 30ºC) prior to the removal of the snap-off cap closure from the powder vial.

Step 1: Remove the cap from the powder vial and clean the top of the stopper with an alcohol swab.
Repeat this step with the solvent vial.
Peel back the top of the transfer device package but leave the device in the package.

Step 2: Place the blue end of the transfer device on the solvent vial and push straight down until the spike penetrates the rubber stopper and snaps into place.
Remove the plastic outer packaging from the transfer device and discard it, taking care not to touch the exposed end of the device.

Step 3: Turn the solvent vial upside down with the transfer device still attached.
Place the clear end of the transfer device on the powder vial and push straight down until the spike penetrates the rubber stopper and snaps into place.

Step 4: The solvent will be pulled into the powder vial by the vacuum contained within it.
Gently swirl the vial to make sure the powder is thoroughly mixed. Do not shake the vial.
A colourless, clear or slightly opalescent solution should be obtained, usually in less than 1 minute (5 minutes maximum).

Step 5: Separate the empty solvent vial and blue part of the transfer device from the clear part by unscrewing anti-clockwise.
Take an empty syringe (not provided in the Coagadex pack) and draw air into it by pulling the plunger to match the volume of water added in step 4. Connect the syringe to the clear part of the transfer device and push the air into the vial.

Step 6: Immediately invert the vial of solution, which will be drawn into the syringe.
Disconnect the filled syringe from the device.
Follow the normal safety practices to administer the medicinal product.

Note: If you have more than one vial to make up your dose, repeat steps 1 through 6 withdrawing the solution in the vial into the same syringe.

The transfer device supplied with the product is sterile and cannot be used more than once. When the reconstitution process is complete, the used transfer device should be disposed of it in the 'sharps box'.

The solution should be colourless, clear or slightly opalescent when administered. Do not use solutions that are cloudy or have deposits. Reconstituted products should be inspected visually for particulate matter and discolouration prior to administration.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BPL Bioproducts Laboratory GmbH
Dornhofstraße 34, 63263 Neu-Isenburg
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1087/001
EU/1/16/1087/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 March 2016
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Bio Products Laboratory Limited
Dagger Lane,
Elstree,
Borehamwood,
WD6 3BX,
United Kingdom

Name and address of the manufacturer responsible for batch release

PNR Pharma Services Limited
Skybridge House
Corballis Road North
Dublin Airport
Swords
Co. Dublin
K67 P6K2
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 250 IU

1. NAME OF THE MEDICINAL PRODUCT

Coagadex 250 IU powder and solvent for solution for injection
human coagulation factor X

2. STATEMENT OF ACTIVE SUBSTANCE(S)

250 IU human coagulation factor X, approximately 100 IU/mL

3. LIST OF EXCIPIENTS

Also contains:
Powder vial: citric acid, sodium hydroxide, disodium phosphate dihydrate, sodium chloride, sucrose.

Solvent vial: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection.

Each pack contains:
1 powder vial
1 transfer device
1 solvent vial of 2.5 mL water for injections

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

Use within 1 hour of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Do not freeze.
Keep the vial in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BPL Bioproducts Laboratory GmbH
63263 Neu-Isenburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1087/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

coagadex 250 iu

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL 250 IU

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Coagadex 250 IU powder for solution for injection
human coagulation factor X

2. METHOD OF ADMINISTRATION

For i.v. use after reconstitution.

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER>

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL 2.5 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 500 IU

1. NAME OF THE MEDICINAL PRODUCT

Coagadex 500 IU powder and solvent for solution for injection
human coagulation factor X

2. STATEMENT OF ACTIVE SUBSTANCE(S)

500 IU human coagulation factor X, approximately 100 IU/mL

3. LIST OF EXCIPIENTS

Also contains:
Powder vial: citric acid, sodium hydroxide, disodium phosphate dihydrate, sodium chloride, sucrose.

Solvent vial: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection.

Each pack contains:
1 powder vial
1 transfer device
1 solvent vial of 5 mL water for injections

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
Use within 1 hour of reconstitution.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Do not freeze.
Keep the vial in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BPL Bioproducts Laboratory GmbH
63263 Neu-Isenburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1087/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

coagadex 500 iu

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL 500 IU

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Coagadex 500 IU powder for solution for injection
human coagulation factor X

2. METHOD OF ADMINISTRATION

For i.v. use after reconstitution

Read the package leaflet before use

3. EXPIRY DATE

EXP:

4. BATCH NUMBER>

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL 5 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Coagadex 250 IU powder and solvent for solution for injection
Coagadex 500 IU powder and solvent for solution for injection

human coagulation factor X

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Coagadex is and what it is used for

Coagadex is a concentrate of human coagulation factor X, a protein that is needed for blood to clot. The factor X in Coagadex is extracted from human plasma (the liquid part of blood). It is used to treat and prevent bleeding in patients with hereditary factor X deficiency, including during surgery.

Patients with factor X deficiency do not have sufficient factor X for their blood to clot properly, leading to excessive bleeding. Coagadex replaces the missing factor X and allows their blood to clot normally.

2. What you need to know before you use Coagadex

Do not use Coagadex:
- if you are allergic to human coagulation factor X or any of the other ingredients of this medicine (listed in section 6).

Check with your doctor if you think this applies to you.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Coagadex:

- if you have a larger or longer bleed than usual and the bleeding does not stop after an injection of Coagadex.
- if you are taking a medicine to prevent blood clotting that works by blocking clotting factor Xa. These medicines may prevent Coagadex from working.

Some patients with a shortage of factor X may develop inhibitors (antibodies) to factor X during treatment. This could mean that the treatment will not work properly. Your doctor will check regularly for the development of these antibodies, and especially before an operation. Both before and after treatment with this medicine, particularly for your first course of treatment, your doctor will probably carry out tests to check the level of factor X in your blood.

Virus safety
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to recipients. These include:

– careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
– the testing of donated plasma for signs of virus/infections,
– the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

The measures taken are considered effective for the following viruses: human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, hepatitis A virus and parvovirus B19. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on an infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

It is strongly recommended that every time you receive a dose of Coagadex, the name and batch number of the product are recorded in order to maintain a record of the batches used.

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly or repeatedly receive human plasma-derived factor X products.

Children and adolescents
The listed warnings and precautions for adults also apply to children (aged 2 to 11 years) and adolescents (aged 12 to 18 years).

Other medicines and Coagadex
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines
There are no known effects of this medicine on the ability to drive or operate machinery.

Coagadex contains sodium
This medicine contains up to 9.2 mg sodium (the main component of cooking/table salt) in each millilitre of solution. This is equivalent to 0.0046% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Coagadex

Your treatment should be initiated by a doctor who is experienced in the treatment of bleeding disorders.

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Coagadex should be injected directly into a vein. Before injecting this medicine at home, you should have received training by your healthcare professional on how to do so.

Your doctor will explain to you how much you should use, when you should use it and for how long. Your doctor will usually tell you your dose in terms of the number of full vials that supply the dose most suited to you. Not more than 60 IU/kg daily should be administered in any age group.

Use in adults

How much Coagadex is given to treat a bleed or prevent further bleeding?
Your doctor will tell you how much Coagadex to administer to treat a bleed and to prevent further bleeding; the dose required will depend on your normal blood level of factor X

How much is given before, during and after major surgery?
Before: The dose of Coagadex used should be sufficient to raise your blood factor X level to between 70 and 90 units/dL. The dose you need will depend on your normal blood level of factor X and will be calculated by your doctor.

After: During the first few days after the operation, your plasma factor X concentration will be checked regularly. It is recommended that your blood factor X level is kept above 50 units/dL. The dose you need will be calculated by your doctor.

If your blood factor X concentration is too low (this will be tested by your doctor), or if it decreases faster than expected, an inhibitor to factor X may be present which stops the medicine from working properly. Your doctor will arrange for the appropriate laboratory tests to see if this is the case.

How much is given regularly for long-term prevention of bleeds?
Your doctor will advise if this use is suitable for you and, if so, of the appropriate dose.

Use in children and adolescents
Your doctor will recommend an appropriate dose for you or your child. Doses for children less than 12 years old are generally larger than for adolescents and adults. Doses for adolescents will be similar to those for adults.

When to inject Coagadex
- The medicine should be injected when the first sign of bleeding occurs.
- The injection should be repeated as necessary to stop the bleeding.
- Each individual bleed should be judged on its own severity.
- If you are using this medicine for the first time, your doctor will supervise you.

Dissolving your medicines before use
Your medicine must **only** be dissolved in the solvent provided with the product.

Quantity of Coagadex	Volume of solvent
250 IU	2.5 mL
500 IU	5 mL

Coagadex is supplied with the amount of solvent as shown in the table.

You can dissolve this medicine using the needle-free Mix2Vial transfer device included within each pack. Bring the containers of Coagadex to room temperature before mixing.
Make up the medicine as follows:

Step 1
• Remove the cap from the powder vial and clean the top of the stopper with an alcohol swab.
• Repeat this step with the vial of solvent.
• Peel back the top of the transfer device package but leave the device in the package.

Step 2
• Place the blue end of the transfer device on the solvent vial and push straight down until the spike penetrates the rubber stopper and snaps into place.
• Remove the plastic outer packaging from the transfer device and discard it, taking care not to touch the exposed end of the device.

Step 3
• Turn the solvent vial upside down with the device still attached.
• Place the clear end of the transfer device on the powder vial and push straight down until the spike penetrates the rubber stopper and snaps into place.

Step 4
• The solvent will be pulled into the powder vial by the vacuum contained within it.
• Gently swirl the vial to make sure the powder is thoroughly mixed. Do not shake the vial.
• A colourless, clear or slightly pearl-like solution should be obtained, usually in about 1 minute (5 minutes maximum).

Step 5
• Separate the empty solvent vial and blue part of the transfer device from the clear part by unscrewing anti-clockwise.
• Take an empty syringe (not provided in the Coagadex pack) and draw air into it by pulling the plunger to match the required volume of water added in step 4.
• Connect the syringe to the clear part of the transfer device and push the air in the syringe into the vial.

Step 6
• Immediately invert the vial of solution, which will be drawn into the syringe.
• Disconnect the filled syringe from the device.
• The product is now ready for use. Follow the normal safety practices for administration. Make sure you use the product within an hour after it has been made up.

Do not use this medicine:

- if the solvent is not pulled into the vial (this indicates loss of vacuum in the vial, so the powder must not be used).

- if the dissolved powder and solvent form a gel or a clot (if this happens please tell your healthcare provider, reporting the batch number printed on the vial).

If you use more Coagadex than you should
If you administer more of this medicine than your doctor prescribed, it is possible you might develop a blood clot. If you think you may be using too much, stop the injection and tell the doctor, pharmacist or nurse. If you know you have used too much, tell the doctor, pharmacist or nurse as soon as possible.

If you forget to use Coagadex
Do not use a double dose to make up for a forgotten dose. Inject your normal dose as you remember and then continue dosing as instructed by your doctor.

If you stop using Coagadex
Always consult your doctor before deciding to stop your treatment.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions (hypersensitivity reactions) have occurred rarely in the treatment of bleeding disorders with similar medicines (affecting up to 1 in 1,000 people), and sometimes progress to shock. Signs of these may include skin rash (including hives), tingling, flushing, nausea, vomiting, headache, cough, wheezing, tightness of the chest, chills, fast heart rate, dizziness, lethargy, restlessness, swelling of the face, tightness of the throat, discomfort at the site of injection.
If you get any of these contact your doctor.

The following side effects have been reported with Coagadex.

Common (may affect up to 1 in 10 people):
- pain or redness at site of injection
- tiredness
- back pain

Side effects in children and adolescents
Side effects in children are expected to be the same as in adults.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Coagadex

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the containers after "EXP". The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not freeze.

Keep container in the outer carton in order to protect it from light.

Do not use this medicine if you notice small bits in the dissolved product. Once made up, Coagadex must be used within one hour.

Do not throw away any medicines via wastewater or household waste. Your treatment centre will provide a special container to dispose of any solution that remains, any used syringes, needles and empty containers. These measures will help protect the environment.

6. Contents of the pack and other information

What Coagadex contains
- The active substance is human coagulation factor X. One vial contains nominally 250 IU or 500 IU human coagulation factor X.
- The other ingredients are: citric acid, disodium phosphate dihydrate, sodium chloride, sodium hydroxide and sucrose (see section 2 for further information about ingredients).
- Solvent: water for injections.

What Coagadex looks like and contents of the pack
Coagadex is a white or off-white powder and is packed in quantities of 250 IU and 500 IU. After being made up, the solution is colourless, clear or pearl-like (opalescent). Before injection, look at the solution. If the solution is cloudy or has any particles, do not use it.

A transfer device called Mix2Vial is also provided.

Contents of the 250 IU pack
1 vial 250 IU powder
1 vial 2.5 mL water for injections
1 Transfer Device (Mix2Vial)

Contents of the 500 IU pack
1 vial 500 IU powder
1 vial 5 mL water for injections
1 Transfer Device (Mix2Vial)

Not all pack sizes may be marketed.

Marketing Authorisation Holder
BPL Bioproducts Laboratory GmbH
Dornhofstraße 34, 63263 Neu-Isenburg
Germany

Manufacturer
PNR Pharma Services Limited, Skybridge House, Corballis Road North, Dublin Airport, Swords, Co. Dublin, K67 P6K2, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu