# COMPANY CORE PACKAGE INSERT – CCPI (PI/CORE/ENGLISH)

# CLUVOT® 250 IU

Rev.: **08-MAY-2014** / New license

**Package leaflet: Information for the user**

# Cluvot® 250 IU

Powder and solvent for solution for injection/infusion.
Human Plasma Coagulation Factor XIII concentrate

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4. for how to report side effects.

**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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


## 1. What Cluvot is and what it is used for

***What is Cluvot?***
Cluvot is presented as white powder and solvent. The made up solution should be given by injection into a vein.

Cluvot is a human plasma coagulation factor XIII (FXIII) product (this is the liquid part of the blood), and has important functions in haemostasis (stopping bleeding).

***What is Cluvot used for?***
Cluvot is used for adult and paediatric patients
- for preventative treatment of inherited FXIII deficiency and
- for peri-operative management of surgical bleeding with congenital FXIII deficiency.

## 2. What you need to know before you are given Cluvot

The following sections contain information that your doctor should consider before you are given Cluvot.

**Do not use Cluvot:**
- if you are allergic to the active substances or any other ingredients of this medicine (listed in section 6).

**Please inform your doctor if you are allergic to any medicine or food.**

**Warnings and precautions**
- if you have experienced allergic reactions on coagulation FXIII in the past. You should take antihistamines and corticosteroids prophylactically if advised by your doctor.
- when allergic or anaphylactic-type reactions occur (a serious allergic reaction that causes severe difficulty in breathing or dizziness). **The administration of Cluvot should then be stopped immediately (e.g. discontinue infusion). In case of shock the current medical standards for shock treatment should be observed.**
- if you have experienced fresh thrombosis (blood clot). Caution should be exercised due to the fibrin-stabilizing effect of FXIII.
- The formation of inhibitors (neutralising antibodies) is a known complication of treatment and it means that the treatment stops working. If your bleeding is not being controlled with Cluvot, tell your doctor immediately. You should be monitored carefully for the development of an inhibitor.

Your doctor will consider carefully the benefit of treatment with Cluvot compared with the risk of these complications.

***Virus safety***
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:
- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A and parvovirus B19 viruses.

It is strongly recommended that every time you receive a dose of Cluvot, your physician should record the name and batch number of the medicine (found on the carton).

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

**Other medicines and Cluvot**
- Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
- No interactions of human plasma coagulation FXIII concentrate with other medicinal products are known.
- Cluvot should not be mixed with other medicinal products, diluents or solvents except those listed in section 6 and it should be administered by a separate infusion line.

**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 you are given this medicine.
- Limited data on the clinical use of Cluvot in pregnancy did not show any negative effects on the course of pregnancy and peri- or postnatal development. Therefore, the use of Cluvot may be considered during pregnancy if necessary.
- There are no data on the excretion of Cluvot into human milk. However, based on its large molecular size excretion into milk is unlikely and due to its proteinaceous character, absorption of intact molecules by the infant is also unlikely. Therefore, Cluvot can be used during breastfeeding.
- No fertility data are available.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed.

**Cluvot contains sodium**
Please take into account that Cluvot contains sodium. This is important, if you are on a controlled sodium diet. Cluvot contains 124.4 to 195.4 mg (5.41 to 8.50 mmol) sodium per dose (40 IU/body weight – for average of 70 kg), if the recommended dose (2800 IU = 44.8 ml ) is applied.

## 3. How to use Cluvot

- Cluvot is usually administered by your doctor.
- Cluvot is intended solely for the injection into a vein.

**Dosage**
Your doctor will calculate the correct dose and will decide on how often Cluvot will be given to you taking into account how well the treatment is working.

For further guidance see section *"The following information is intended for medical or healthcare professionals only"*.

***Overdose***
No cases of overdose have been reported and are not expected since healthcare professionals administer the medicine.

## 4. Possible side effects

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

The following side effects have been observed **rarely** (affects more than 1 user in 10,000 and less than 1 user in 1,000):
- Allergic reactions, such as generalised urticaria (itchy swellings on the skin), rash, fall in blood pressure (which could make you feel faint or dizzy) and difficulty breathing.
- Rise in temperature

The following side effects have been observed **very rarely** (affects less than 1 user in 10,000):
- Development of inhibitors to FXIII.

If **allergic reactions** occur, the administration of Cluvot must be discontinued immediately and an appropriate treatment initiated. The current medical standards for shock treatment should be observed.

**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, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.
[For EU only: You can also report side effects directly via the national reporting system listed in Appendix V QRD template]

## 5. How to store Cluvot

- Store in a refrigerator (+2°C to +8°C).
- Do not freeze.
- Keep the vial in the outer carton, in order to protect from light.
- Cluvot contains no preservatives. The product must be used immediately after reconstitution. If not used immediately, storage shall not exceed 4 hours at room temperature. Do not refrigerate or freeze the reconstituted solution.

- **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 label and carton.

## 6. Contents of the pack and other information

### What Cluvot contains

***The active substance is:***
Human Plasma Coagulation Factor XIII concentrate containing 250 IU per vial.

***The other ingredients are:***
Human albumin, glucose monohydrate, sodium chloride, sodium hydroxide (in small amounts for pH adjustment)
*Solvent:* Water for Injections

### What Cluvot looks like and contents of the pack
Cluvot is presented as a white powder and is supplied with a solvent (Water for Injections).
The made-up solution should be colourless, clear to slightly opalescent. When held up to the light it should not be cloudy or contain residues (deposits/particles).

***Presentation***
One pack with 250 IU containing:
- 1 vial with powder
- 1 vial with 4 ml water for injections
- 1 filter transfer device 20/20 (Mix2Vial)

### Marketing Authorisation Holder and Manufacturer
CSL Behring GmbH
Emil-von-Behring-Strasse 76
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Germany

**This leaflet was last revised in May 2014.**

**The following information is intended for healthcare professionals only:**

## Posology and method of administration

### *Posology*

1 ml is equivalent to approximately 62.5 IU, and 100 IU are equivalent to 1.6 ml, respectively.
Important:
The amount to be administered and the frequency of administration should always be oriented towards the clinical efficacy in the individual case.

### *Dosage*

The dosing regimen should be individualized based on body weight, laboratory values, and the patient's clinical condition.

Routine Prophylaxis Dosing Schedule
Initial dose

- 40 International Units (IU) per kg body weight
- The injection rate should not exceed 4 ml per minute.

Subsequent dosing

- Dosing should be guided by the most recent trough FXIII activity level, with dosing every 28 days (4 weeks) to maintain a trough FXIII activity level of approximately 5 to 20%.
- Recommended dosing adjustments of ±5 IU per kg should be based on trough FXIII activity levels as shown in Table 1 and the patient's clinical condition.
- Dosing adjustments should be made on the basis of a specific, sensitive assay used to determine FXIII levels. An example of dose adjustment using the standard Berichrom® activity assay is outlined in Table 1 below.

Table 1: Dose Adjustment Using the Berichrom® Activity Assay

| Factor XIII Activity Trough Level (%) | Dosage Change |
|---|---|
| One trough level of < 5% | Increase by 5 units per kg |
| Trough level of 5% to 20% | No change |
| Two trough levels of > 20% | Decrease by 5 units per kg |
| One trough level of > 25% | Decrease by 5 units per kg |

The potency expressed in units is determined using the Berichrom® activity assay, referenced to the current International Standard for Blood Coagulation Factor XIII, Plasma. Therefore, a unit herein is equivalent to an International Unit.

Prophylaxis Prior to Surgery
After the patient's last routine prophylactic dose, if a surgery is scheduled:

- Between 21 and 28 days later – administer the patient's full prophylaxis dose immediately prior to surgery and the next prophylactic dose should be given 28 days later.

- Between 8 and 21 days later – an additional dose (full or partial) may be administered prior to surgery. The dose should be guided by the patient's FXIII activity levels and clinical condition and should be adjusted according to the half-life of Cluvot
- Within 7 days of last dose – additional dosing may not be needed.

Adjustments to dosing may be different than these recommendations and should be individualized based on FXIII activity levels and the patient's clinical condition. All patients should be monitored closely during and after surgery.

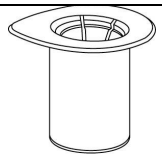
Thus, it is recommended to monitor the increase in FXIII-activity with a FXIII-assay. In the case of major surgery and severe haemorrhages the aim is to obtain near normal values (healthy persons: 70% - 140%).

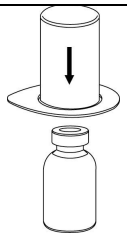
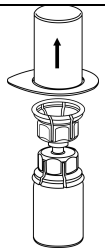
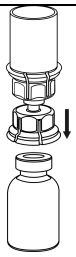
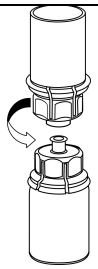
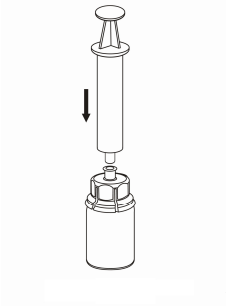
***Paediatric population***
The posology and method of administration in children and adolescents is based on body weight and is therefore generally based on the same guidelines as for adults. The dose and/or frequency of administration for each individual should always be guided by the clinical effectiveness and FXIII activity levels.

***Elderly population***
The posology and method of administration in elderly people (> 65 years) has not been documented in clinical studies.

***Method of administration***
*General instructions*
- The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- Do not use visibly cloudy solutions or solutions still containing flakes or particles.
- Reconstitution and withdrawal must be carried out under aseptic conditions.

*Reconstitution*
Bring the solvent to room temperature. Ensure product and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

| | |
|---|---|
|  1 | 1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package! |

| | |
|---|---|
|  2 | 2. Place the **solvent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight down** through the solvent vial stopper. |
|  3 | 3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set. |
|  4 | 4. Place the **product vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial. |
|  5 | 5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew counterclockwise the set carefully into two pieces.<br>Discard the solvent vial with the blue Mix2Vial adapter attached. |
|  6 | 6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake. |
|  7 | 7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting. Inject air into the product vial. |

*Withdrawal and application*

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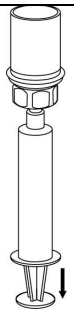
|---|---|
|  8 | 8. While keeping the syringe plunger pressed, invert the system upside down and draw the solution into the syringe by pulling the plunger back slowly. |
|  9 | 9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise. |

Care should be taken that no blood enters the syringe filled with product, as there is a risk that the blood could coagulate in the syringe and fibrin clots would therefore be administered to the patient.

**The reconstituted solution should be administered intravenously** by a separate injection / infusion line by slow injection at a rate not exceeding 4 ml per minute.

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