ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cablivi 10 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 10 mg of caplacizumab*.
Each pre-filled syringe of solvent contains 1 mL of water for injections.

* Caplacizumab is a humanised bivalent Nanobody produced in *Escherichia coli* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White lyophilised powder.
The solvent is a clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cablivi is indicated for the treatment of adults and adolescents of 12 years of age and older weighing at least 40 kg experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.

4.2 Posology and method of administration

Treatment with Cablivi should be initiated and supervised by physicians experienced in the management of patients with thrombotic microangiopathies.

Posology

First dose

Intravenous injection of 10 mg of caplacizumab prior to plasma exchange.

Subsequent doses

Daily subcutaneous administration of 10 mg of caplacizumab after completion of each plasma exchange for the duration of daily plasma exchange treatment, followed by daily subcutaneous injection of 10 mg of caplacizumab for 30 days after stopping daily plasma exchange treatment.

If at the end of this period there is evidence of unresolved immunological disease, it is recommended to optimise the immunosuppression regimen and continue daily subcutaneous administration of 10 mg of caplacizumab until the signs of underlying immunological disease are resolved (e.g. sustained normalisation of ADAMTS13 activity level).

In the clinical development program, caplacizumab has been administered daily for up to 71 days consecutively. Data on re-treatment with caplacizumab are available (see section 5.1).

Missed dose

If a dose of Cablivi is missed, it can be administered within 12 hours. If more than 12 hours have passed since the dose was to have been given, the missed dose should NOT be administered and the next dose should be administered per the usual dosing schedule.

Special populations

Renal impairment
No dose adjustment is necessary for patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with hepatic impairment (see section 5.2). See section 4.4 for special considerations in patients with severe hepatic impairment.

Elderly
While experience with the use of caplacizumab in the elderly is limited, there is no evidence to suggest that dose adjustment or special precautions are needed for elderly patients (see section 5.2).

Paediatric population
The safety and efficacy of caplacizumab in the paediatric population have not been established in clinical studies. The posology of Cablivi in adolescents of 12 years of age and older weighing at least 40 kg is the same as in adults (see section 5.2). No recommendations can be made on the posology of Cablivi for paediatric patients below 40 kg of body weight.

Method of administration

The first dose of Cablivi is to be administered as an intravenous injection. Subsequent doses are to be administered via subcutaneous injection in the abdomen.

Injections into the area around the navel should be avoided and consecutive injections should not be administered in the same abdominal quadrant.

Patients or caregivers may inject the medicinal product after proper training in the subcutaneous injection technique.

For instructions on reconstitution of Cablivi 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 the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Bleeding

Cablivi increases the risk of bleeding. Cases of major bleeding, including life-threatening and fatal bleeding have been reported in patients receiving caplacizumab, mainly in those using concomitant anti-platelet agents or anticoagulants. Caplacizumab should be used with caution in patients with underlying conditions that may predispose them to a higher risk of bleeding

In case of clinically significant bleeding, treatment with Cablivi should be interrupted. If needed, the use of von Willebrand Factor concentrate could be considered to correct hemostasis. Cablivi should only be restarted upon the advice of a physician experienced in the management of thrombotic microangiopathies. If Cablivi is restarted, monitor closely for signs of bleeding.

In the setting of concomitant use of oral anticoagulants, anti-platelet agents, thrombolytic agents or heparin
The risk of bleeding is increased with concomitant use of Cablivi with other medicinal products affecting hemostasis and coagulation. Initiation or continuation of treatment with oral anticoagulants (e.g., vitamin K antagonists or direct oral anticoagulants [DOAC] such as thrombin inhibitors or factor Xa inhibitors), anti-platelet agents, thrombolytic agents such as urokinase, tissue plasminogen activator (t-PA) (e.g. alteplase) or heparin requires careful consideration and close clinical monitoring.

In patients with coagulopathies
Due to a potential increased risk of bleeding, use of Cablivi in patients with underlying coagulopathies (e.g. hemophilia, other coagulation factor deficiencies) must be accompanied by close clinical monitoring.

In patients undergoing surgery
If a patient is to undergo elective surgery, an invasive dental procedure or other invasive interventions, the patient must be advised to inform the physician or dentist that they are using caplacizumab and it is recommended to withhold treatment for at least 7 days before the planned intervention. The patient must also notify the physician who supervises the treatment with caplacizumab about the planned procedure. After the risk of surgical bleeding has resolved, and caplacizumab is resumed, the patient should be monitored closely for signs of bleeding.

If emergency surgery is needed, the use of von Willebrand Factor concentrate is recommended to correct haemostasis.

Severe hepatic impairment

No formal study with caplacizumab has been conducted in patients with severe acute or chronic hepatic impairment and no data regarding the use of caplacizumab in these populations are available. Use of Cablivi in this population requires a benefit/risk assessment and close clinical monitoring.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies evaluating use of caplacizumab with oral anticoagulants (e.g. vitamin K antagonists, direct oral anticoagulants [DOAC] such as thrombin inhibitors or factor Xa inhibitors), antiplatelet agents, thrombolytic agents such as urokinase, tPA (e.g. alteplase) or heparin have been performed (see section 4.4 *In the setting of concomitant use of oral anticoagulants, anti-platelet agents, thrombolytic agents or heparin).*

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of caplacizumab in pregnant women. Studies in guinea pigs showed no effect of caplacizumab on the dams or foetuses (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of Cablivi during pregnancy.

Breastfeeding

There are no data on the use of caplacizumab in breastfeeding women. It is unknown whether caplacizumab is excreted in human milk. A risk to the child cannot be excluded.
A decision must be made whether to discontinue breastfeeding or to abstain/discontinue from therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

The effects of caplacizumab on fertility in humans are unknown. In animal toxicology studies, no impact of caplacizumab on male and female fertility parameters was observed (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions in the TITAN and HERCULES clinical studies were epistaxis, headache and gingival bleeding. The most common serious adverse reaction was epistaxis.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA system organ class and by frequency. Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data).

Table 1 . List of adverse reactions in TITAN and HERCULES studies

MedDRA System organ class	Very common	Common
Nervous system disorders	Headache	Cerebral infarction
Eye disorders		Eye Haemorrhage*
Vascular disorders		Haematoma*
Respiratory, thoracic and mediastinal disorders	Epistaxis*	Dyspnoea, Haemoptysis*
Gastrointestinal disorders	Gingival bleeding*	Haematemesis*, haematochezia*, melaena*, upper gastrointestinal haemorrhage*, haemorrhoidal haemorrhage*, rectal haemorrhage *, abdominal wall haematoma*
Skin and subcutaneous tissue disorders	Urticaria	
Musculoskeletal and connective tissue disorders		Myalgia
Renal and urinary disorders		Haematuria*
Reproductive system and breast disorders		Menorrhagia*, vaginal haemorrhage*
General disorders and administration site conditions	Pyrexia, Fatigue	Injection site haemorrhage*, injection site pruritus, injection site erythema, injection site reaction
Injury, poisoning and procedural complications		Subarachnoid haemorrhage*

*Bleeding events: see below

Description of selected adverse reactions

Bleeding

In clinical studies, bleeding events occurred in different body systems, independent of treatment duration. In the postmarketing setting, cases of major bleeding, including life-threatening and fatal bleeding have been reported in patients receiving caplacizumab, mainly in those using concomitant anti-platelet agents or anticoagulants. In case of clinically significant bleeding, consider actions outlined in sections 4.4 and 4.9.

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

In case of overdose, based on the pharmacological action of caplacizumab, there is the potential for an increased risk of bleeding. Close monitoring for signs and symptoms of bleeding is recommended. (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antithrombotic agents, ATC code: B01AX07.

Mechanism of action

Caplacizumab is a humanised bivalent Nanobody that consists of two identical humanised building blocks (PMP12A2hum1), genetically linked by a three-alanine linker, targeting the A1-domain of von Willebrand factor and inhibiting the interaction between von Willebrand factor and platelets. As such, caplacizumab prevents the ultra large von Willebrand factor-mediated platelet adhesion, which is characteristic of aTTP. It also affects the disposition of von Willebrand factor, leading to transient reductions of total von Willebrand factor antigen levels and to concomitant reduction of factor VIII:C levels during treatment.

Pharmacodynamic effects

Target inhibition

The pharmacologic effect of caplacizumab on target inhibition was assessed using two biomarkers for von Willebrand factor activity; ristocetin-induced platelet aggregation (RIPA) and ristocetin cofactor (RICO). Full inhibition of von Willebrand factor-mediated platelet aggregation by caplacizumab is indicated by RIPA and RICO levels dropping below 10% and 20%, respectively. All clinical studies with caplacizumab demonstrated rapid decreases in RIPA and/or RICO levels after the start of the treatment, with recovery to baseline levels within 7 days of discontinuation. The 10 mg subcutaneous dose in patients with aTTP elicited full inhibition of von Willebrand factor-mediated platelet aggregation, as evidenced by RICO levels of < 20% throughout the treatment period.

Target disposition

The pharmacologic effect of caplacizumab on target disposition was measured using von Willebrand factor antigen and factor VIII clotting activity (factor VIII:C) as biomarkers. Upon repeated administration of caplacizumab, a decrease of 30-50% in von Willebrand factor antigen levels was observed in clinical studies, reaching a maximum within 1-2 days of treatment. Because von Willebrand factor acts as a carrier for factor VIII, reduced von Willebrand factor antigen levels resulted in a similar reduction in factor VIII:C levels. The reduced von Willebrand factor antigen and FVIII:C levels were transient and returned to baseline upon cessation of treatment.

Clinical efficacy and safety

The efficacy and safety of caplacizumab in adults experiencing an episode of aTTP were established in 3 randomised, controlled studies: Phase III study ALX0681-C301 “HERCULES”, Phase III study ALX0681-C302 “Post-HERCULES” and Phase II study ALX-0681-2.1/10 “TITAN”.

Efficacy

Study ALX0681-C301 (HERCULES)
In this double-blind, placebo-controlled study, patients with an episode of aTTP were randomised 1:1 to receive either caplacizumab or placebo in addition to daily plasma exchange and immunosuppression. Patients received a single intravenous bolus injection of 10 mg caplacizumab or placebo prior to the first plasma exchange on study. This was followed by daily subcutaneous injections of 10 mg caplacizumab or placebo after completion of each plasma exchange for the duration of the daily plasma exchange period and for 30 days thereafter. If at the end of this treatment period there was evidence of persistent underlying disease activity (indicative of an imminent risk for recurrence), treatment could be extended weekly for a maximum of 4 weeks, together with

optimisation of immunosuppression. If a recurrence occurred while on study drug treatment, patients were switched to open-label caplacizumab. They were again treated for the duration of daily plasma exchange and for 30 days thereafter. If at the end of this treatment period there was evidence of ongoing underlying disease, open-label treatment with caplacizumab could be extended weekly for a maximum of 4 weeks, together with optimisation of immunosuppression. Patients were followed for 1 month after discontinuation of treatment. In case of recurrence during the follow up period (i.e. after all study drug treatment had been stopped), there was no re-initiation of study drug and the recurrence was to be treated according to the standard of care.

In this study, 145 patients experiencing an episode of aTTP were randomised (72 to caplacizumab and 73 to placebo). Patient age ranged from 18 to 79 years, with a mean of 46 years. Half of the patients were experiencing their first episode of aTTP. Baseline disease characteristics were typical of aTTP.

The median treatment duration with caplacizumab in the double blind period was 35 days.

Treatment with caplacizumab resulted in a statistically significant reduction in time to platelet count response ($p<0.01$). Patients treated with caplacizumab were 1.55 times more likely to achieve platelet count response at any given time point, compared to patients treated with placebo.

Treatment with caplacizumab resulted in a 74% reduction in the composite endpoint of the percentage of patients with aTTP-related death (0/72; placebo 3/73), exacerbation of aTTP (3/72; placebo 28/73), or at least one major thromboembolic event during study drug treatment (6/72; placebo 6/73) ($p<0.0001$). There were no deaths in the caplacizumab group and 3 deaths in the placebo group during the study drug treatment period.

The proportion of patients with a recurrence of aTTP (exacerbation or relapse) in the overall study period (including the 28 day follow-up after discontinuation of study drug treatment) was 67% lower in the caplacizumab group (9/72; relapse : 6/72) compared to the placebo group (28/73; relapse 0/73) ($p<0.001$).

No patients treated with caplacizumab (0/72) were refractory to treatment (defined as absence of platelet count doubling after 4 days of standard treatment and elevated LDH) compared to three patients treated with placebo (3/73).

Treatment with caplacizumab reduced the mean number of days of plasma exchange, the volume of plasma used, the mean length of Intensive Care Unit stay and the mean length of hospitalization during the study drug treatment period.

Table 2. Summary of number of days of plasma exchange (PE), total volume of PE used, number of days in hospital and ICU in the ITT population

		Placebo	Caplacizumab
Number of days of Plasma Exchange (days)	N Mean (SE)	73 9.4 (0.81)	71 5.8 (0.51)
Total volume of plasma used (litre)	N Mean (SE)	73 35.93 (4.17)	71 21.33 (1.62)
Length of hospitalization (days)	N Mean (SE)	73 14.4 (1.22)	71 9.9 (0.70)
Number of days in ICU	N Mean (SE)	27 9.7 (2.12)	28 3.4 (0.40)

N: number of patients evaluated; SE: Standard Error; ICU: Intensive Care Unit

Study ALX0681-C302 (Post-HERCULES)
The Post-HERCULES study was a Phase III, 36-month follow-up study from HERCULES (parent study) to evaluate the long-term outcomes as well as the safety and efficacy of repeat use of caplacizumab in patients who experienced a recurrence of aTTP. Overall, 104 out of 108 patients who completed the parent study (75 who received caplacizumab in HERCULES, of whom 49 did not have aTTP recurrences prior to the enrollment in Post-HERCULES, and 29 who had received only standard

of care (SoC) in HERCULES) entered the Post-HERCULES study in which patients attended twice yearly visits. Patients could receive open-label (OL) caplacizumab for the treatment of an aTTP recurrence along with SoC.

Overall, 19 patients had at least 1 recurrence of aTTP and six patients had a 2nd recurrence. For patients treated with caplacizumab for a recurrence, all events of aTTP from the first recurrence episode were resolved or were resolving at the end of the study.

The overall safety profile of caplacizumab re-treatment was consistent with that observed in other clinical studies of aTTP.

Immunogenicity

In clinical studies, up to 11% of patients developed treatment-emergent anti-drug antibodies (ADA). No impact on clinical efficacy was observed and no serious adverse events were found to be associated with these ADA responses.

Paediatric population

See section 4.2 for information on paediatric use and section 5.2 for results of modelling and simulation studies for paediatric patients. There are no clinical data for paediatric patients.

5.2 Pharmacokinetic properties

The pharmacokinetics of caplacizumab have been investigated in healthy subjects after single intravenous infusions and after single and repeated subcutaneous injections. Pharmacokinetics in patients with aTTP were investigated upon single intravenous and repeated subcutaneous injections.

Pharmacokinetics of caplacizumab appear as non-dose proportional, as characterized by target-mediated disposition. In healthy volunteers receiving 10 mg caplacizumab subcutaneously once daily, the maximum concentration was observed at 6-7 hours post-dose and steady-state was reached following the first administration, with minimal accumulation.

Absorption

After subcutaneous administration, caplacizumab is rapidly and almost completely absorbed (estimated F> 0.901) in the systemic circulation.

Distribution

After absorption, caplacizumab binds to the target and distributes to well perfused organs. In patients with aTTP the central volume of distribution was estimated at 6.33 L.

Biotransformation/Elimination

The pharmacokinetics of caplacizumab depend on the expression of the target von Willebrand factor. Higher levels of von Willebrand factor antigen, such as in patients with aTTP, increase the fraction of drug-target complex retained in the circulation. The $t_{1/2}$ of caplacizumab is, therefore, concentration- and target level-dependent. Target-bound caplacizumab is assumed to be catabolised within the liver, whereas unbound caplacizumab is assumed to be renally cleared.

Characteristics in specific groups

The pharmacokinetics of caplacizumab were determined using a population pharmacokinetic analysis on pooled pharmacokinetic data. Body weight was allometrically included in the model. Differences in the different subpopulations were investigated. In studied populations; gender, age, blood group and race did not affect the pharmacokinetics of caplacizumab.

Renal or hepatic impairment

No formal study of the effect of hepatic or renal impairment on the pharmacokinetics of caplacizumab has been conducted. In the population PK/PD model, renal function (CRCL) had a statistically significant effect resulting in limited increase in predicted exposure (AUCss) in severe renal impairment. In the clinical studies of patients with TTP, those with renal impairment did not show additional risk of adverse events.

Paediatric population

Based on data pooled from clinical studies in adults, a pharmacokinetic-pharmacodynamic (PK/PD) population model was developed, describing the interaction between caplacizumab and von Willebrand factor antigen (vWF:Ag), in different adult populations following intravenous and subcutaneous administration of caplacizumab at various dose levels. For children aged 2 to below 18 years of age, simulations were performed based on this PK/PD model predicting that exposure and suppression of vWF:Ag are expected to be similar to those in adults when 10 mg/day is used in children with a bodyweight of ≥40 kg, and when 5 mg/day is used in children with a bodyweight of <40 kg.

5.3 Preclinical safety data

Consistent with its mode of action, toxicology studies of caplacizumab have shown an increased bleeding tendency in guinea pigs (haemorrhagic subcutaneous tissue at the injection sites) and cynomolgus monkeys (haemorrhagic subcutaneous tissue at the injection sites, nose bleed, exaggerated menstrual bleeding, haematoma at sites of animal handling or experimental procedures, prolonged bleeding at injection sites). Furthermore, pharmacology-related decreases of von Willebrand factor antigen, and consequently factor VIII:C, were noted in cynomolgus monkeys and, to a lesser extent for factor VIII:C, in guinea pigs.

An embryo-foetal development study was conducted in guinea pigs, with no reported signs of toxicity. A follow-up toxicokinetic study in pregnant guinea pigs assessed exposure of caplacizumab in the dams and foetuses. The results indicated exposure to caplacizumab in dams and, to a much lesser extent, foetuses, with no reported effects on foetal development. Foetal exposure to caplacizumab in primates and humans remains uncertain, as proteins lacking an Fc portion are not thought to freely pass the placental barrier.

No studies have been performed to evaluate the mutagenic potential of caplacizumab, as such tests are not relevant for biologicals. Based on a carcinogenicity risk assessment, dedicated studies were not deemed necessary.

Dedicated animal studies assessing the effects of caplacizumab on male and female fertility have not been performed. In repeat-dose toxicity tests in cynomolgus monkeys, no impact of caplacizumab on fertility parameters in male (testicular size, sperm function, histopathological analysis of testis and epididymis) and female (histopathological analysis of reproductive organs, periodic vaginal cytology) animals was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sucrose
Citric acid anhydrous (E 330)
Trisodium citrate dihydrate (E 331)

Polysorbate 80

Solvent

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, Cablivi must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

5 years.

Reconstituted solution

Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C.
From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Store in the original package in order to protect from light.

Cablivi may be stored at a temperature not above 25 °C for a single period of up to 2 months, but not beyond the expiry date. Do not return Cablivi to refrigerated storage after storage at room temperature.

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

6.5 Nature and contents of container

Powder

Vial (type I glass) with a stopper (butyl rubber), a seal (aluminium) and a cap (polypropylene), containing 10 mg of caplacizumab.

Solvent

Pre-filled syringe (type I glass cartridge closed with a bromobutyl rubber stopper) with 1 mL of water for injections.

Pack size

- Single pack containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter, 1 hypodermic needle (30 gauge) and 2 alcohol swabs.
- Multipack containing 7 single packs.
- Multidose pack containing 7 vials with powder, 7 pre-filled syringes with solvent, 7 vial adapters, 7 hypodermic needles (30 gauge) and 14 alcohol swabs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For both intravenous and subcutaneous administration, reconstitute the powder contained in the vial using the vial adapter and all solvent in the pre-filled syringe. The solvent should be added slowly and mixed gently to avoid foaming of the solution. Allow the vial with connected syringe to stand on a surface for 5 minutes at room temperature.

The reconstituted solution is clear, colourless, or slightly yellowish. It must be visually inspected for particulate matter. Do not use solution exhibiting particulates.

Transfer the entire volume of the reconstituted solution back to the glass syringe and immediately administer the entire volume of the syringe (see section 6.3).

Cablivi is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ablynx NV
Technologiepark 21
9052 Zwijnaarde
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1305/001
EU/1/18/1305/002
EU/1/18/1305/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 August 2018
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
Richter-Helm BioLogics GmbH & Co. KG
Dengelsberg
24796 Bovenau
Germany

Name and address of the manufacturer responsible for batch release
Ablynx NV
Technologiepark 21
9052 Zwijnaarde
Belgium

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).

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.

- **Additional risk minimisation measures**

Prior to launch of Cablivi in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the patient alert card, including communication media, distribution modalities, and any other aspects, with the National Competent Authority.
The MAH shall ensure that in each Member State where Cablivi is marketed, all patients/carers who are expected to use Cablivi are provided with the following patient alert card which shall contain the following key message:

- to mitigate the risk of serious bleeding episode particularly in emergency situations (e.g. accident) to inform physicians about the medical blockage of the von Willebrand Factor.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cablivi 10 mg powder and solvent for solution for injection
caplacizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial of powder contains 10 mg caplacizumab.
Eachpre-filled syringe of solvent contains 1 mL of water for injections.

3. LIST OF EXCIPIENTS

Excipients: sucrose, citric acid anhydrous, trisodium citrate dihydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Content:
1 vial with powder
1 syringe with solvent
1 sterile vial adapter
1 sterile needle
2 alcohol swabs

Content :
7 vials with powder
7 syringes with solvent
7 sterile vial adapters
7 sterile needles
14 alcohol swabs

5. METHOD AND ROUTE OF ADMINISTRATION

For single use only
Read the package leaflet before use
Intravenous and subcutaneous 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

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original package in order to protect from light.

Cablivi may be stored at room temperature (not above 25 °C) for a single period of up to 2 months.

Date removed from refrigerator: _____

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

Ablynx NV
Technologiepark 21
9052 Zwijnaarde, Belgium

12. MARKETING AUTHORISATION NUMBERS

EU/1/18/1305/001
EU/1/18/1305/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cablivi

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON
Multipack (contains Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Cablivi 10 mg powder and solvent for solution for injection
caplacizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial of powder contains 10 mg caplacizumab.
Each pre-filled syringe of solvent contains 1 mL of water for injections.

3. LIST OF EXCIPIENTS

Excipients: sucrose, citric acid anhydrous, trisodium citrate dihydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Multipack: 7 packs of 1 single dose kit.

5. METHOD AND ROUTE OF ADMINISTRATION

For single use only
Read the package leaflet before use
Intravenous and subcutaneous 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

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original package in order to protect from light.

Cablivi may be stored at room temperature (not above 25 °C) for a single period of up to 2 months.

Date removed from refrigerator: _____

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

Ablynx NV
Technologiepark 21
9052 Zwijnaarde
Belgium

12. MARKETING AUTHORISATION NUMBERS

EU/1/18/1305/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cablivi

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON
Multipack (without Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Cablivi 10 mg powder and solvent for solution for injection
caplacizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial of powder contains 10 mg caplacizumab.
Each pre-filled syringe of solvent contains 1 mL of water for injections.

3. LIST OF EXCIPIENTS

Excipients: sucrose, citric acid anhydrous, trisodium citrate dihydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Content:
1 vial with powder
1 syringe with solvent
1 sterile vial adapter
1 sterile needle
2 alcohol swabs

Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Intravenous and subcutaneous use
For single use only

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

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original package in order to protect from light.

Cablivi may be stored at room temperature (not above 25 °C) for a single period of up to 2 months.

Date removed from refrigerator: _____

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

Ablynx NV
Technologiepark 21
9052 Zwijnaarde
Belgium

12. MARKETING AUTHORISATION NUMBERS

EU/1/18/1305/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cablivi

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

Cablivi 10 mg powder for solution for injection
caplacizumab
IV and SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT SYRINGE LABEL

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

Solvent for Cablivi

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL water for injections

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Cablivi 10 mg powder and solvent for solution for injection
caplacizumab

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 Cablivi is and what it is used for

Cablivi contains the active substance caplacizumab. It is used to treat an episode of **acquired thrombotic thrombocytopenic purpura** in adults and adolescents of 12 years of age and older weighing at least 40 kg. This is a rare blood clotting disorder in which clots form in small blood vessels. These clots can block blood vessels and damage the brain, heart, kidneys, or other organs. Cablivi prevents the formation of these blood clots by stopping platelets in the blood from clumping together. By doing so, Cablivi reduces the risk of experiencing another episode of aTTP soon after the first.

2. What you need to know before you use Cablivi

Do not use Cablivi
- if you are allergic to caplacizumab or any of the other ingredients in this medicine (listed in section 6)

Warnings and precautions

Tell your doctor if you:
- bleed excessively or experience unusual symptoms such as headache, shortness of breath, tiredness, or fainting which may indicate serious internal bleeding. Your doctor may ask you to stop the treatment. The doctor will say when you can start your treatment again.
- are using medicines that prevent or treat blood clots such as warfarin, heparin, rivaroxaban, apixaban. Your doctor will decide how you should be treated.
- are using anti-platelet agents such as aspirin, or low molecular weight heparin (which prevent blood clots). Your doctor will decide how you should be treated.
- have a bleeding disorder such as haemophilia. Your doctor will decide how you should be treated.
- have severely reduced liver function. Your doctor will decide how you should be treated.
- are going to have an operation or dental treatment. Your doctor will decide if it can be postponed or if you should stop Cablivi before your surgery or dental treatment.

Children and adolescents
Cablivi is not recommended for children under 12 years and below 40 kg body weight.

Other medicines and Cablivi
Tell your doctor or pharmacist if you are using, have recently used, or might use any other medicines.

Also tell your doctor if you are using an anticoagulant medicine such as vitamin K antagonists, rivaroxaban, or apixaban which treat blood clots or anti-platelet agents, such as aspirin, or low molecular weight heparin which prevent blood clots.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or plan to get pregnant. Use of Cablivi is not recommended during pregnancy.

Tell your doctor if you are breastfeeding. Your doctor will advise you whether to discontinue breastfeeding or not use Cablivi, considering the benefit of breastfeeding to the baby and the benefit of Cablivi to you.

Driving and using machines
Cablivi is not expected to influence the ability to drive or use machines.

Cablivi contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use Cablivi

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

Treatment with Cablivi is started by a doctor experienced in blood disorders.

The recommended treatment is

- **first dose**
  - 1 vial injected into a vein by a healthcare professional
  - the medicine will be given before starting plasma exchange.

- **subsequent doses**
  - 1 vial once daily as a subcutaneous injection (under the skin of the belly)
  - the subcutaneous injection will be given after each daily plasma exchange
  - after the daily plasma exchange finishes, your treatment with Cablivi will continue for at least 30 days with injection of 1 vial once daily
  - your doctor may ask you to continue daily treatment until the underlying signs of your disease are resolved.

Your doctor may decide that you or your caregiver may inject Cablivi. In this case, your doctor or healthcare provider will train you or your caregiver on how to use Cablivi.

Instructions for use
The first injection of Cablivi into your vein must be given by a healthcare professional. Instructions for healthcare professionals on how to inject Cablivi into your vein are at the end of the leaflet.

For each injection, use a fresh kit package to prepare the injection solution. Do not try to inject Cablivi until you have been taught how to do so by a healthcare professional. Never use the kit for another injection.

Step 1 - Cleaning

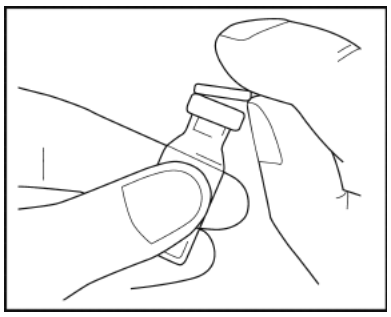
- Wash your hands thoroughly with soap and water.
- Prepare a clean flat surface for placing the kit package.
- Make sure you have a disposal container at hand.

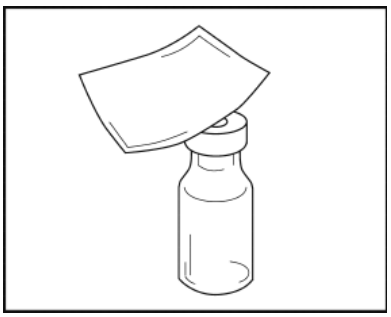
Step 2 - Before use

- Make sure the kit package is complete.
- **Check the expiry date**. Do not use if the expiry date has passed.
- Do not use the kit if the packaging or the items in it are damaged in any way.
- Place all components of the kit on the clean flat surface.
- If the kit was not stored at room temperature, allow the vial and the syringe to reach room temperature (15°C – 25°C) by letting them stand at room temperature for a few minutes. Do not warm them up in any other way.

Step 3 - Disinfect the rubber stopper

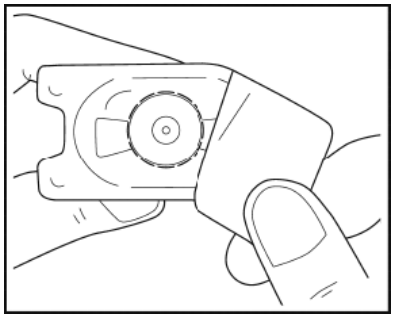
- Remove the plastic flip-off cap from the vial. Do not use the vial if the green plastic cap is missing.
- Clean the exposed rubber stopper using one of the alcohol pads provided and allow it to dry for a few seconds.
- After cleaning, do not touch the rubber stopper or allow it to touch any surface.



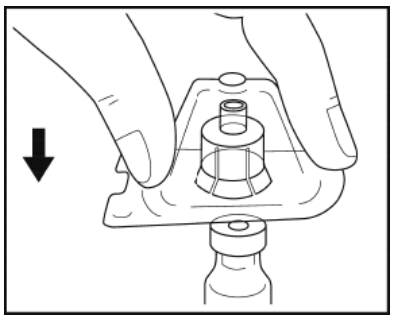


Step 4 - Attaching the adapter

- Take the packed vial adapter and remove the paper cover. Leave the adapter in its opened plastic packaging. Do not touch the adapter itself.

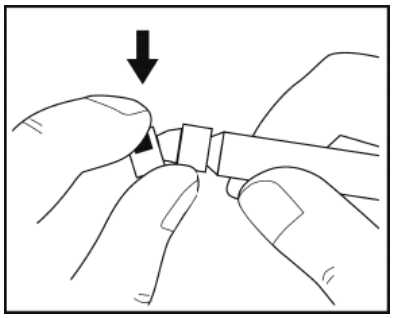


- Place the adapter over the vial, while keeping the adapter in its plastic packaging.
- Press down firmly until the adapter snaps into place, with the adapter spike going through the vial stopper. Leave the adapter attached to the vial, **still in its outer packaging.**



Step 5 - Prepare the syringe

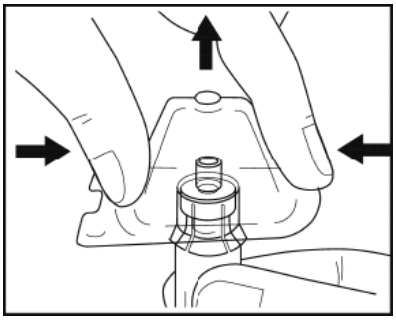
- Holding the syringe in your hand, break off the white cap with your other hand.
- Do not use the syringe if this white cap is missing, loose or damaged.



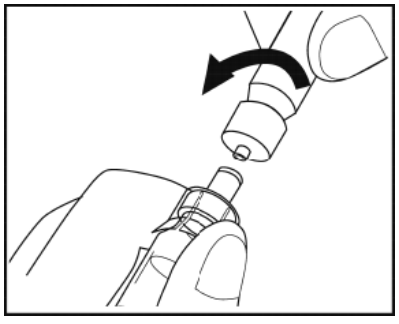
- **Do not touch** the syringe tip or allow it to come into contact with any surfaces.
- Place the syringe on the clean flat surface.

Step 6 - Connect syringe with adapter and vial

- Take the vial with the attached adapter.
- Remove the plastic packaging from the adapter by holding the vial with one hand, pressing the sides of the adapter packaging with your other hand, and then lifting the packaging upwards. Take care that the adapter does not come away from the vial.

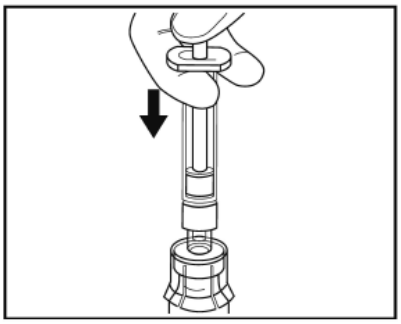


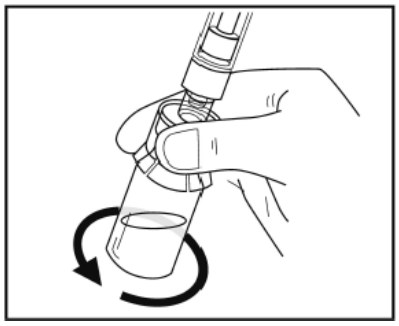
- Hold the adapter with the attached vial with one hand. Place the tip of the syringe on the connector part of the vial adapter.
- Gently lock the syringe onto the vial by turning it clockwise until resistance is felt.



Step 7 - Prepare the solution

- Keep the vial standing vertically on the surface with the syringe pointing downwards.
- Slowly push the syringe's plunger down until the syringe is empty. Do not remove the syringe from the vial.
- With the syringe still connected to the vial adapter, gently swirl the vial with connected syringe until the powder is dissolved. Avoid foaming. **Do not shake** the vial.

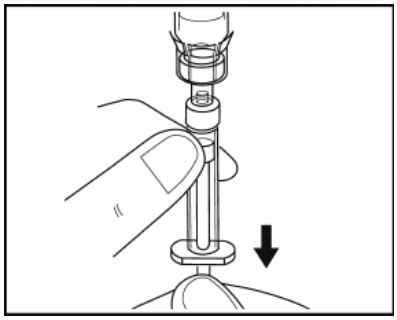




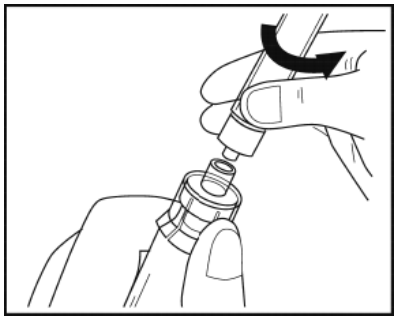
- Allow the vial with connected syringe to stand on the surface for **5 minutes** at room temperature to allow the solution to completely dissolve. The plunger may rise up by itself again - this is normal.
- Go to step 8 immediately after these 5 minutes.

Step 8 - Draw up solution

- **Check the solution** for particles. All powder must be dissolved and the solution must be clear.
- Slowly press the syringe's plunger fully down.
- Turn the whole - vial, adapter and syringe - upside down.
- While keeping it vertical, slowly pull the plunger to transfer all the solution into the syringe. Do not shake it.



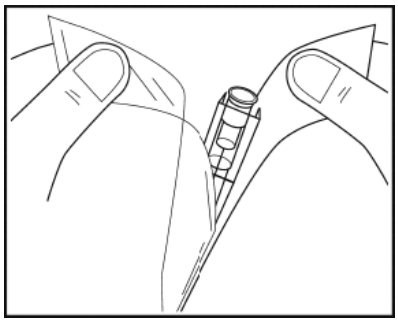
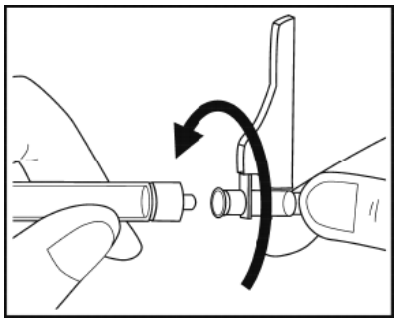
Step 9 - Prepare the syringe for administration



- Turn the whole - vial, adapter and syringe - right-side up (with the syringe at the top). Disconnect the filled syringe from the adapter by holding the adapter in one hand and gently turning the syringe counter-clockwise.
- Put the vial and the attached adapter into the supplied disposal container.
- **Do not touch** the syringe tip or allow it to touch the surface. Place the syringe on the clean flat surface.

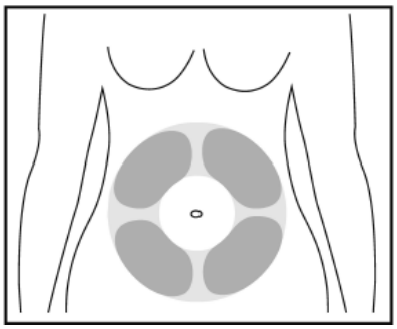
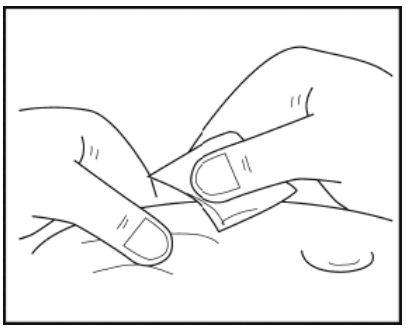
- Go to step 10 to inject caplacizumab under the skin of the belly. Instructions for healthcare professionals on how to inject Cablivi into your vein are at the end of the leaflet.

Step 10 - Attach the needle
- Unpack the needle by tearing the paper cover off the needle packaging and removing the needle with protective cap.

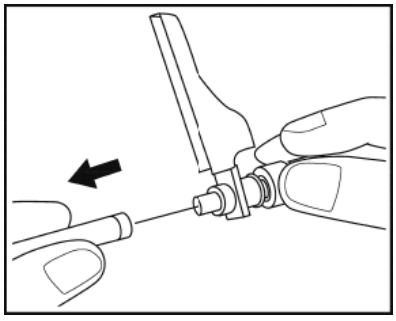
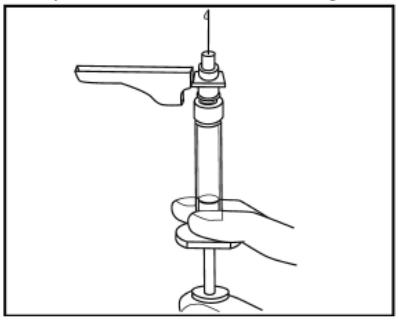
- Without removing the needle cap, attach the needle to the syringe by turning clockwise until resistance is felt.
- Pull back the needle safety shield.
- **Check the content of the syringe**. Do not use the medicine if you see any cloudiness, clumps or anything else that looks abnormal. Contact your doctor or nurse if this happens.

Step 11 - Prepare injection site for injection under the skin

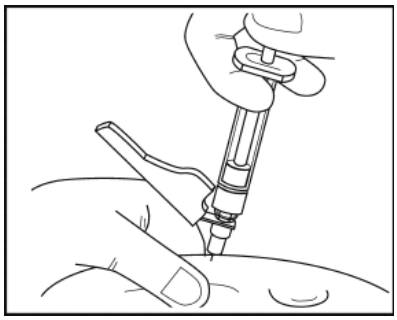



- Select a suitable place (‘injection site’) on your belly for injection under your skin. Avoid the area around the belly button. Select a different injection site from the one you used on the previous day to help the skin to recover after the injection.'
- Use the second alcohol pad to clean the injection site you have chosen.

Step 12 - Administration
- Carefully remove the needle protection cap from the needle and throw it away. Make sure the needle does not touch anything before the injection.
- Hold the syringe at eye level with the needle pointing upwards.
- Remove any air bubbles by tapping the side of the syringe with your finger to make the bubbles rise towards the tip. Then, slowly push the plunger until a small amount of liquid comes out of the needle.
- Gently pinch the cleaned skin between your thumb and forefinger to make a fold.

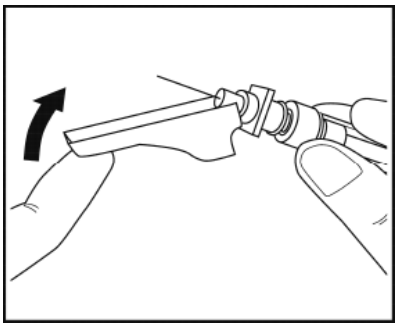



- Hold this skin fold during the entire injection.
- Insert the full length of the needle into the skin fold at an angle as shown in the illustration.
- Press the plunger down as far as it goes.



- Pull out the needle at the same angle you inserted it. Do not rub the injection site.

Step 13 - After administration
- Immediately after the injection, move the needle safety shield over the needle, until it clicks into place.



- Put the syringe with the needle in a disposal container.

If you use more Cablivi than you should
An overdose is unlikely since one vial contains only a single dose. Tell your doctor if you think you have had an overdose.

If you forget to use Cablivi
If you miss a dose you should still take it if it is within 12 hours of the scheduled time. If more than 12 hours have passed since the dose should have been given, do not take the missed dose, but inject the next dose at the usual time.

If you stop using Cablivi
To get the most benefit from your treatment, it is important to use Cablivi as prescribed and for as long as your doctor tells you to use it. Please talk to your doctor before you stop the treatment because stopping it too early can cause your condition to come back.

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

4. Possible side effects

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

Contact your doctor immediately if any of the following serious side effects occur.
Long or excessive bleeding.
Your doctor may decide to keep you under closer observation or change your treatment.

Side effects in a clinical study were reported with the following frequencies:

Very common, may affect more than 1 in 10 people
- bleeding gums
- fever
- tiredness
- headache
- nosebleeds
- hives

Common, may affect up to 1 in 10 people
- bleeding from eye
- vomiting blood
- blood in the stools
- black, tarry stools
- bleeding from the stomach
- bleeding hemorrhoids
- rectal bleeding
- injection site reactions: rash, itching and bleeding
- bleeding in brain as evidenced by severe headache of rapid onset, vomiting, decreased level of consciousness, fever, sometimes seizures and neck stiffness or neck pain
- muscle pain
- stroke
- blood in urine
- excessive bleeding during periods
- vaginal bleeding
- coughing blood
- shortness of breath
- bruise

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 Cablivi

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 after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C - 8 °C). Do not freeze.
Store in the original package in order to protect from light.

Cablivi may be stored at a temperature not above 25 °C for a single period of up to 2 months, but not beyond the expiry date. Do not return Cablivi to refrigerated storage after storage at room temperature. Never expose to temperatures above 30 °C.

Do not use Cablivi if you notice any particulate matter or discolouration prior to administration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cablivi contains

- **powder vial**
  - The active substance is caplacizumab.
    Each vial contains 10 mg caplacizumab.
  - The other ingredients are sucrose, citric acid anhydrous, trisodium citrate dihydrate (see section 2 “Cablivi contains sodium”) and polysorbate 80.
- **pre-filled syringe**
  The pre-filled syringe contains 1 mL water for injections.

What Cablivi looks like and contents of the pack

Cablivi is provided as:
- a white powder for solution for injection in a glass vial, and
- water for injections in a pre-filled syringe to dissolve the powder

After dissolving the powder in the solvent, the solution is clear, colourless or slightly yellowish.

Cablivi is available in
- single packs each containing 1 vial with caplacizumab powder, 1 pre-filled syringe with solvent, 1 vial adapter, 1 needle and 2 alcohol swabs
- multipacks each containing 7 single packs
- multidose packs each containing 7 vials with caplacizumab powder, 7 pre-filled syringes with solvent, 7 vial adapters, 7 needles and 14 alcohol swabs.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Ablynx NV
Technologiepark 21
9052 Zwijnaarde
Belgium

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

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel.: 0800 04 36 996
Tel. aus dem Ausland: +49 69 305 70 13

Nederland
Genzyme Europe B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
sanofi-aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Ísland
Vistor hf.
Sími: +354 535 7000

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Italia
Sanofi S.r.l.
Tel: 800 536389

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in.

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

The following information is intended for healthcare professionals only:

The intravenous bolus injection of Cablivi given at the start of the treatment must be administered by a health care professional. Preparing a dose of Cablivi for intravenous injection should be done in the same way as for a subcutaneous injection (see Instructions for Use, step 1 to 9, in section 3).

Cablivi can be intravenously administered by connecting the prepared syringe to standard Luer locks of intravenous lines or using a suitable needle. The line can be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection.