1. NAME OF THE MEDICINAL PRODUCT

Cablivi

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 S.C, IV.

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

Patient safety information Card

The marketing of Cablivi is subject to a risk management plan (RMP) including a 'Patient safety information card'. The Patient safety information card' emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cablivi is indicated for the treatment of adults 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 after initial treatment course, sign(s) of persistent underlying disease such as suppressed ADAMTS13 activity levels remain present, treatment may be extended for a maximum of 28 days.

In the clinical development program, caplacizumab has been administered daily for up to 65 days. No data on re-treatment with caplacizumab are available.

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
Cablivi is not indicated for children and adolescents under 18 years old
The safety and efficacy of caplacizumab in the paediatric population have not yet been established. No data are available.

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

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 drugs or heparin
The risk of bleeding is increased with concomitant use of Cablivi with drugs 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 drugs 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 hemostasis.

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.

Traceability
In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

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 drugs 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 drugs 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 trials 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).

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

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 ultralarge 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 2 randomised, controlled studies: Phase III study ALX0681-C301 “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.

		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 (liter)	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

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.

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 subcutaneoulsy 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.

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
Trisodium citrate dihydrate
Citric acid anhydrous
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

The expiry date of the product is indicated on the packaging materials.

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.
- 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 subcutaneuous 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 AND IMPORTER AND ITS ADDRESS

Sanofi-aventis Israel Ltd. 10 Beni Gaon St., POB 8090, Netanya

9. LICENSE NUMBER

165-25-36110-00

Revised in February 2023 according to MoH guidelines.