Date: 8 November 2019
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Cablivi

International non-proprietary name: caplacizumabum
Pharmaceutical form: Powder and solvent for solution for injection
Dosage strength: 10 mg
Route(s) of administration: Subcutaneous use, Intravenous use
Marketing Authorisation Holder: Sanofi-Aventis (Suisse) SA
Marketing Authorisation No: 66792
Decision and Decision date: approved on 01.10.2019

Note:

Assessment Report as adopted by Swissmedic with all information of commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices TPA (SR 812.21). The agency ensures that only high quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products TPO (SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibodies
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
Max	Maximum
MAH	Marketing Authorisation Holder
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PSP	Pediatric Study Plan (US-FDA)
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 1 or 2 of the TPA. The Orphan Status was granted on 26 October 2017.

Authorisation human medical product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA. The reduced assessment procedure was accepted on 28 January 2019.

2.2 Indication and Dosage

2.2.1 Requested Indication

Cablivi is used for the treatment of adults suffering from an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasmapheresis and immunosuppression.

2.2.2 Approved Indication

Cablivi is used for the treatment of adults suffering from an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasmapheresis and immunosuppression.

2.2.3 Requested Dosage

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 optimize 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 65 days. No data on re-treatment with caplacizumab are available.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	3 January 2019
Formal control completed	28 January 2019
Predecision	7 May 2019
Answers to Predecision	4 July 2019
Final Decision	1 October 2019

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Decision	approval

Swissmedic has not assessed the primary data of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency EMA. The current SwissPAR refers to the publicly available Assessment Report Cablivi, EMEA/H/C/004426/0000, dated 28 June 2018 of the European Medicines Agency EMA.

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3 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency EMA. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report Cablivi, EMEA/H/C/004426/0000, dated 28 June 2018 of the European Medicines Agency EMA.

4 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency EMA. The current SwissPAR relating to preclinical aspects refers to the publicly available Assessment Report Cablivi, EMEA/H/C/004426/0000, dated 28 June 2018of the European Medicines Agency EMA.

5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency EMA. The current SwissPAR relating to clinical aspects refers to the publicly available Assessment Report Cablivi, EMEA/H/C/004426/0000, dated 28 June 2018 of the European Medicines Agency EMA.

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the Information for healthcare professionals relating to Cablivi 10 mg, Powder and solvent for solution for injection was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference documents, which are valid and relevant for the effective and safe use of medicinal products in Switzerland, are the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The MAH is responsible for the correct translation of the text. Only the Information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or severe adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Cablivi 10 mg powder and solvent for solution for injection

Composition

Vial with powder:
Active substance: Caplacizumab*
Excipients: Saccharose, anhydrous citric acid, sodium citrate-dihydrate, Polysorbate 80.
* Caplacizumab is a humanised, bivalent nanobody produced in *Escherichia coli* using recombinant DNA technology.

Pre-filled syringe with solvent:
Water for injections

Pharmaceutical form and active substance quantity per unit

Powder and solvent for solution for injection (i.v., s.c.).
Vial with powder: 10 mg caplacizumab as a white, lyophilised powder.
Solvent: 1 ml water for injections as a clear, colourless liquid.
Reconstitution with 1 ml water for injections produces a concentration of 10 mg/ml caplacizumab.

Indications/Uses

Cablivi is used for the treatment of adults suffering from an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasmapheresis and immunosuppression.

Dosage/Administration

Treatment with Cablivi should be started and monitored by physicians with experience in the management of patients with thrombotic microangiopathies.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade

name and batch number should be documented for each treatment.

Posology

First dose

Intravenous injection of 10 mg caplacizumab before plasmapheresis.

Subsequent doses

Daily subcutaneous administration of 10 mg caplacizumab after conclusion of each plasmapheresis for the duration of the daily plasmapheresis treatment, then daily subcutaneous injection of 10 mg caplacizumab for 30 days after the end of the daily plasmapheresis treatment.

If signs of an immunological disease remain at the end of this period, it is recommended to optimise the immunosuppression regime and to continue the daily subcutaneous administration of 10 mg caplacizumab until the signs of the underlying immunological disease have receded (e.g. permanent normalisation of the ADAMTS13 activity level).

Caplacizumab was administered daily for up to 65 days in the clinical development program. There are no data available regarding restarting caplacizumab therapy.

Forgotten dose

If a dose of Cablivi is forgotten, it can be made up for within 12 hours. If it has been longer than 12 hours since the previous dose, the missed dose should NOT be administered and the next dose should be administered according to the usual dosage schedule.

Special dosage recommendations

Patients with impaired renal function

No dose adjustment is required in patients with impaired renal function (see "Pharmacokinetics").

Patients with impaired hepatic function

No dose adjustment is required in patients with impaired hepatic function (see "Pharmacokinetics"). See "Warnings and precautions" regarding special considerations for patients with severely impaired hepatic function.

Elderly patients

Although there is limited experience regarding the use of caplacizumab in elderly patients, there are no indications that a dose adjustment or special precautions are required in elderly patients (see "Pharmacokinetics").

Children and adolescents
The safety and efficacy of caplacizumab have not yet been demonstrated in children and adolescents. No data are available.

Mode of administration

The initial dose of Cablivi is to be administered as an intravenous injection.
After reconstitution of Cablivi (see "Other information"), the solution for injection can be administered intravenously by connecting the prepared syringe via standardised Luer lock connections with infusion lines or an appropriate needle. The line can be rinsed with 0.9% sodium chloride.
Subsequent doses are to be administered as subcutaneous injections to the abdomen. Injections around the navel should be avoided and consecutive injections should not be administered in the same abdominal quadrant.
After appropriate instruction in subcutaneous injection technique, the medicinal product may be injected by the patient or a carer.
For instructions on the reconstitution of Cablivi before use, see "Other information".

Contraindications
Hypersensitivity to the active substance or one of the excipients listed in the composition.

Warnings and precautions
Bleeding

Active, clinically relevant bleeding
Treatment with Cablivi should be discontinued in the event of active, clinically relevant bleeding. If required, the use of a von Willebrand factor concentrate to correct the haemostasis may be considered. Treatment with Cablivi should only be restarted on the advice of a physician with experience in the management of thrombotic microangiopathies.

Increased risk of bleeding

For the concomitant use of oral anticoagulants or high-dosed heparin

Owing to a potentially increased risk of bleeding, the initiation or continuation of the treatment with oral anticoagulants or high-dosed heparin requires a risk-benefit assessment and close clinical monitoring.

For the concomitant use of platelet aggregation inhibitors and/or low molecular weight heparin (LMWH)

Although no increased risk of bleeding was observed in clinical trials, the concomitant treatment with platelet aggregation inhibitors and/or LMWH requires a risk-benefit assessment and close clinical monitoring.

In patients with coagulopathies

Owing to a potentially increased risk of bleeding, the use of Cablivi in patients with underlying coagulopathies (e.g. haemophilia, other coagulation factor deficiencies) must be combined with close clinical monitoring.

In patients undergoing surgery

If a patient is to undergo elective surgery or a dental procedure, the patient should be advised to inform the physician or dentist that they are using Cablivi and to discontinue the therapy at least 7 days before the planned procedure. The patient should also inform the physician monitoring the Cablivi treatment of the planned procedure. If emergency surgery is required, the use of a von Willebrand factor concentrate to correct the haemostasis may be considered.

Severely impaired hepatic function

No formal study has been performed regarding caplacizumab in patients with acute or chronic severely impaired hepatic function. There are no data available regarding the use of caplacizumab in these populations. The use of Cablivi in these populations requires a risk-benefit assessment and close clinical monitoring.

Cablivi contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is practically "sodium-free".

Interactions

No studies have been performed to record the interactions during concomitant use of caplacizumab and oral anticoagulants (e.g. vitamin K antagonists or direct oral anticoagulants [DOAC] such as thrombin inhibitors or factor Xa inhibitors) or high-dosed heparin (see "Warnings and precautions / For concomitant use of oral anticoagulants or high-dosed heparin").

Pregnancy, lactation

Pregnancy

There are insufficient data available on the use of caplacizumab in pregnant patients. Caplacizumab may increase the risk of bleeding in pregnant women, foetuses and newborns. Pregnant women and newborns are to be monitored for any signs of strong bleeding (see "Warnings and precautions"). Studies in guinea pigs showed no effect of caplacizumab on the mothers or foetuses (see "Preclinical data"). As a precaution, the use of Cablivi should be avoided during pregnancy.

Lactation

There are insufficient data available on the use of caplacizumab in lactating patients. It is not known if caplacizumab passes into the breast milk. A risk for the child cannot be excluded.

It must be decided whether breastfeeding is to be stopped or the treatment avoided/discontinued. In so doing, account must be taken of the benefit of breastfeeding for the child as well as the benefit of the therapy for the woman.

Fertility

The effects of caplacizumab on fertility in humans are not known. In toxicological animal studies, no effect of caplacizumab on male and female fertility parameters was observed (see "Preclinical data").

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The most common undesirable effects in clinical trials were epistaxis (29%), headaches (21%), bleeding gums (16%), fatigue (15%), urticaria (14%) and fever (13%). The most common severe undesirable effect was epistaxis.

Tabular listing of undesirable effects

The undesirable effects are shown per system organ class in accordance with MedDRA. The frequency categories are defined as follows: very common (≥1/10), common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), unknown (frequency cannot be estimated on the basis of the available data).

System organ class	**Very common**	**Common**
Nervous system disorders	Headaches	Cerebral infarct
Eye disorders		Eye bleeding*
Vascular disorders		Haematoma*
Respiratory, thoracic and mediastinal disorders	Epistaxis*	Dyspnoea, haemoptysis*
Gastrointestinal disorders	Bleeding gums*	Haematemesis*, haematochezia*, melaena*, upper gastrointestinal tract bleeding*, haemorrhoidal bleeding*, rectal bleeding*, 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 bleeding*
General disorders and administration site conditions	Fever, fatigue	Bleeding at the injection site*, itching at the injection site, erythema at the injection site, reaction at the injection site
Injury, poisoning and procedural		Subarachnoidal bleeding*

complications		

*Bleeding events: see below

Description of selected undesirable effects

Bleeding

Cablivi increases the risk of bleeding. In clinical studies, severe bleeding events such as epistaxis, bleeding gums, bleeding in the upper gastrointestinal tract and metrorrhagia were each reported in 1% of patients, respectively. Bleeding occurred in 58% of patients receiving Cablivi overall, compared to 43% of patients receiving placebo.

Although these events were severe and necessitated medical treatment in some cases, the majority were self-limiting and all abated. In the event of active, clinically relevant bleeding, the measures described under "Warnings and precautions" are to be considered.

Reporting of suspected undesirable effects

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is an increased risk of bleeding in the event of an overdose owing to the pharmacological effect of caplacizumab. Close monitoring of the signs and symptoms of bleeding is recommended (see "Warnings and precautions").

Properties/Effects

ATC code: B01AX07.

Mechanism of action

Caplacizumab is a humanised, bivalent nanobody composed of two humanised subunits (PMP12A2hum1) which are genetically combined using a 3-alanine linker.
It targets the A1 domain of von Willebrand factor and inhibits the interaction between von

Willebrand factor and thrombocytes. Caplacizumab thus prevents thrombocyte adhesion mediated by ultra-large von Willebrand factor which is characteristic of aTTP. It influences the availability of von Willebrand factor, leading to a temporary reduction of the overall antigen level of von Willebrand factor and to the concurrent reduction of the factor VIII:C level during treatment.

Pharmacodynamics

Target inhibition

The pharmacological 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). The complete inhibition by caplacizumab of the platelet aggregation mediated by von Willebrand factor is shown by the levels of RIPA and/or RICO falling below 10% or 20%, respectively. All clinical studies with caplacizumab showed rapid reduction of the levels of RIPA and/or RICO after the initiation of treatment, whereby the levels returned to the baseline value 7 days after discontinuing the therapy. The subcutaneous dose of 10 mg in patients with aTTP led to complete inhibition of the platelet aggregation mediated by von Willebrand factor, shown by the level of RICO falling below 20% for the entire duration of the treatment.

Target distribution

The pharmacological effect of caplacizumab on target distribution was measured using the von Willebrand factor antigen and factor VIII coagulation activity (factor VIII:C) as biomarkers. A 30-50% reduction of the level of von Willebrand factor antigen was reported in clinical studies for the repeated administration of caplacizumab, whereby the treatment reached the maximum value within the first 1-2 days. As von Willebrand factor functions as a carrier for factor VIII, reduced levels of von Willebrand factor led to a similar reduction in the level of factor VIII:C. The reduction in the levels of von Willebrand factor and factor VIII:C was temporary and these returned to baseline levels after discontinuation of the therapy.

Clinical efficacy and safety

The efficacy and safety of caplacizumab in adults who are experiencing an episode of aTTP were demonstrated in two randomised, controlled studies: the Phase III ALX0681-C301 "HERCULES" study and the Phase II ALX-0681-2.1/10 "TITAN" study.

Efficacy

Study ALX0681-C301

In this double-blind, placebo-controlled study, patients with an episode of aTTP were randomised at a ratio of 1:1 to receive either caplacizumab or placebo as an addition to daily plasmapheresis and immunosuppression. The patients received a single intravenous bolus injection of 10 mg caplacizumab or placebo before the first plasmapheresis in the context of the study. This was followed by daily subcutaneous injections of 10 mg caplacizumab or placebo after the conclusion of each plasmapheresis for the duration of the daily plasmapheresis period and for 30 days beyond this. If there were indications of continuing activity of the underlying disease at the end of the treatment period (indicative of an immediate risk of relapse), the treatment could be prolonged for a week for up to a maximum of 4 weeks together with optimisation of the immunosuppression. If a relapse occurred under treatment, the patients were switched to open-label caplacizumab. They were then treated again for the duration of the daily plasmapheresis and for 30 days beyond this. If there were indications of persistent underlying disease at the end of the treatment period, the open-label treatment with caplacizumab could be prolonged for a week for up to a maximum of 4 weeks together with optimisation of the immunosuppression. The patients were followed for 1 month after discontinuation of the therapy. In the event of a relapse during the follow-up period (i.e. after the end of the relevant treatment with the investigational product), treatment with the investigational product was not restarted and the relapse required treatment according to the standard of care.

A total of 145 patients who experienced an episode of aTTP were randomised in this study (72 to caplacizumab and 73 to placebo). The patients ranged from 18-79 years of age, whereby the average was 46 years of age. Half of the patients were experiencing their first episode of aTTP. The disease characteristics at baseline were typical for aTTP.

The median duration of treatment with caplacizumab in the double-blind section was 35 days.

Treatment with caplacizumab led to a statistically significant reduction in the time to platelet count response ($p < 0.01$). Patients who were treated with caplacizumab had a 1.55-fold higher likelihood at each time-point of achieving a platelet count response than patients treated with placebo.

Treatment with caplacizumab led to a 74% reduction in the composite endpoint of the proportion of patients with aTTP-related death (0/72, placebo: 3/73), aTTP exacerbation (3/72, placebo:

28/73) or at least one severe thromboembolic event (6/72, placebo: 6/73) (p <0.0001). There were no fatalities in the caplacizumab group and three in the placebo group during the treatment phase with the investigational product.

The proportion of patients with an aTTP recurrence (exacerbation or relapse) in the overall study period (including the 28-day follow up after discontinuation of treatment with the investigational product) 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).

Compared to three patients treated with placebo (3/73), no patients treated with caplacizumab (0/72) were refractory to treatment (defined as the absence of the doubling of the platelet count after 4-day standard treatment and elevated LDH).

Treatment with caplacizumab reduced the mean number of days with plasmapheresis, the plasma volume used, the mean duration in the intensive care unit and the mean duration of hospitalisations during the treatment period with the investigational product.

		Placebo	Caplacizumab
Number of days with plasmapheresis (days)	N	73	71
	Mean (SE)	9.4 (0.81)	5.8 (0.51)
Total volume of plasma used (litres)	N	73	71
	Mean (SE)	35.93 (4.17)	21.33 (1.62)
Duration of hospitalisations (days)	N	73	71
	Mean (SE)	14.4 (1.22)	9.9 (0.70)
Number of days in intensive care unit	N	27	28
	Mean (SE)	9.7 (2.12)	3.4 (0.40)

N: number of patients investigated, SE: standard error

Immunogenicity

Within the clinical studies, up to 9% of patients developed treatment-related anti-drug antibodies (ADA). No effect on the clinical efficacy was observed, nor severe undesirable effects in connection with these ADA reactions.

Children and adolescents

See "Dosage/Administration" regarding instructions for use in children and adolescents.

Pharmacokinetics

The pharmacokinetics of caplacizumab were investigated in healthy study participants after single intravenous infusions as well as after single and repeated subcutaneous injections. The pharmacokinetics in patients with aTTP were investigated after single intravenous and repeated subcutaneous injections.

The pharmacokinetics of caplacizumab were shown not to be dose-proportional, as shown by the target-mediated distribution. In healthy volunteers who received 10 mg caplacizumab subcutaneously daily, the maximum concentration was observed 6-7 hours after administration of the dose and the steady state was achieved with minimal accumulation after the initial administration.

Absorption

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

Distribution

After resorption, caplacizumab binds to the target and is distributed to well-perfused organs. In patients with aTTP, the central distribution volume is estimated at 6.33 litres.

Metabolism/Elimination

The pharmacokinetics of caplacizumab are dependent on the expression of the target, von Willebrand factor. Higher levels of von Willebrand factor antigen, as occur in patients with aTTP, increase the proportion of drug-target complex stored in the circulation. The $t_{1/2}$ of caplacizumab is thus dependent on the concentration and target level. Target-bound caplacizumab is presumably metabolised via the liver, whereas unbound caplacizumab is presumably excreted via the kidneys.

Kinetics of special patient groups

The pharmacokinetics of caplacizumab were determined by pooled pharmacokinetic data using a pharmacokinetic population analysis. Body weight was included in the model allometrically. Differences between the various subpopulations were investigated. Sex, age, blood group and ethnicity had no influence on the pharmacokinetics of caplacizumab in the populations

investigated.

Impaired hepatic or renal function

No formal studies on the effects of impaired hepatic or renal function on the pharmacokinetics of caplacizumab have been performed. Renal function (CRCL) had a statistically significant effect in the population-based PK/PD model, namely a limited increase of the predicted exposure (AUCss) for severely impaired renal function. In clinical studies in patients with TTP, no additional risk for undesirable effects was observed for patients with impaired renal function.

Preclinical data

In concordance with its mechanism of action, toxicological studies of caplacizumab demonstrated an increased tendency toward bleeding in guinea pigs (haemorrhagic subcutaneous tissue at the injection site) and macaques (haemorrhagic subcutaneous tissue at the injection site, nosebleeds, excessive menstrual bleeding, haematomas at contact or investigation sites, persistent bleeding at the injection sites). Furthermore, pharmacology-related reductions of the von Willebrand factor antigen and thus of factor VIII:C were determined in macaques and, to a lesser extent, with regard to factor VIII:C, in guinea pigs.

One study on embryo-foetal development was performed in guinea pigs, whereby no signs of toxicity were observed. A toxicokinetic follow-up study in pregnant guinea pigs assessed the exposure to caplacizumab of the mothers and foetuses. The results indicated an exposure to caplacizumab in the mothers and, to a considerably lesser extent, in the foetuses, whereby no effects were observed on foetal development. The foetal exposure to caplacizumab in primates and humans remains unclear as proteins which do not have an Fc fragment are presumably not free to cross the placental barrier.

No studies have been performed to assess the mutagenic potential as such tests are not relevant for biologicals. On the basis of the carcinogenic risk assessment, dedicated studies were not considered to be necessary.

Dedicated animal studies to assess the effects of caplacizumab on male and female fertility parameters have not been performed. No effects of caplacizumab on fertility parameters were observed in male animals (testicle size, sperm function, histopathological analysis of the testes and epididymis) and female animals (histopathological analysis of the reproductive organs, cyclical vaginal cytology) in toxicity tests with repeated dose administration in macaques.

Other information

Incompatibilities

As no incompatibility studies have been performed, Cablivi must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Reconstituted solution

The reconstituted solution for injection is not preserved. The chemical and physical stability after opening have been demonstrated for a period of 4 hours at 25 °C. For microbiological reasons, the ready-to-use preparation should be used immediately after reconstitution, except if the reconstitution is performed under controlled, aseptic conditions. If this is not possible, in-use storage times and conditions are the responsibility of the user.

Special precautions for storage

Keep out of the reach of children.
Store in the refrigerator (2-8 °C).
Do not freeze.
Store in the original packaging to protect the contents from light.

Cablivi can be stored at a maximum temperature of 25 °C for a single period of up to 2 months, however not beyond the expiry date. Cablivi must not be returned to the refrigerator after storing at room temperature.

For storage conditions after reconstitution of the medicinal product, see "Shelf life".

Instructions for handling

For both intravenous and subcutaneous administration, the powder in the vial must be reconstituted with the entire solvent in the pre-filled syringe using the vial adapter. The solvent should be added slowly and mixed carefully to prevent the solution from foaming. Allow the vial with syringe connected to stand at room temperature for 5 minutes.

The reconstituted solution is clear, colourless or slightly yellow. It must be visually inspected for

particles. The solution must not be used if it contains particles.

Transfer the entire volume of the reconstituted solution back into the glass syringe and administer the entire volume in the syringe immediately (see "Shelf life").

Cablivi is intended for single use only. Unused medicinal product or waste material is to be disposed of according to national guidelines.

Marketing authorisation number

66792 (Swissmedic)

Packs

Pack of 1 vial. The pack contains:

- 1 vial with powder
- 1 pre-filled syringe with solvent
- 1 vial adapter
- 1 injection needle (30 G)
- 2 alcohol swabs

[B]

Marketing authorisation holder

sanofi-aventis (suisse) sa, 1214 Vernier

Date of revision of the text

October 2019