

Attachment 1: Product information for AusPAR - CABLIVI - caplacizumab - Sanofi-Aventis Australia Pty Ltd - PM-2019-02057-1-6 FINAL 5 May 2020. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION – CABLIVI (CAPLACIZUMAB)

1 NAME OF THE MEDICINE

Caplacizumab

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 List of excipients.

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 experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.

4.2 DOSE 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 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.

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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 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 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 in one patient only. Discard any residue.

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. In clinical studies, severe bleeding adverse reactions of epistaxis, gingival bleeding, upper gastrointestinal haemorrhage, and metrorrhagia were each reported in 1% of subjects. Overall, bleeding events occurred in approximately 58% of patients on CABLIVI versus 43% of patients on placebo.

Active clinically significant bleeding

In case of active, clinically significant bleeding, treatment with Cablivi should be interrupted. If needed, the use of von Willebrand Factor-containing concentrate could be considered to correct haemostasis. Cablivi should only be restarted upon the advice of a physician experienced in the management of thrombotic microangiopathies.

Increased risk of bleeding

In the setting of concomitant use of oral anticoagulants or high dose heparin

Due to a potential increased risk of bleeding, initiation or continuation of treatment with oral anticoagulants or high dose heparin requires a benefit/risk assessment and close clinical monitoring.

In the setting of concomitant use of anti-platelet agents and / or low molecular weight heparin (LMWH)

While no increased risk of bleeding was observed in clinical trials, concomitant treatment with anti-platelet agents and / or LMWH requires a benefit/risk assessment 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. haemophilia, other coagulation factor deficiencies) is to be accompanied by 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 treatment should be stopped at

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least 7 days before the planned intervention. The patient should also notify the physician who supervises the treatment with Cablivi about the planned procedure.

If emergency surgery is needed, the use of von Willebrand Factor concentrate could be considered 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.

Use in the 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 use

The safety and efficacy of caplacizumab in the paediatric population have not yet been established. No data are available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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) or high dose heparin have been performed (See Section 4.4 *In the setting of concomitant use of oral anticoagulants or high dose heparin*).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of caplacizumab on fertility in humans are unknown. No effects on sperm or male or female reproductive tissues to suggest impairment of fertility were observed in cynomolgus

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monkeys receiving caplacizumab at subcutaneous doses up to 40 mg/kg/day, yielding almost 40 times the plasma AUC in patients at the maximum recommended clinical dose of 10 mg/day. Functional fertility studies have not been performed with caplacizumab in animals.

Use in pregnancy (Category B1)

There are no adequate and well-controlled studies with Cablivi in pregnant women. No adverse effects on embryofetal development were observed with caplacizumab in guinea pigs at intramuscular doses up to 20 mg/kg/day, yielding 50 times the plasma AUC in patients at the maximum recommended clinical dose. Limited placental transfer of caplacizumab was shown in guinea pigs.

Cablivi should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the fetus. All patients receiving Cablivi, including pregnant women, are at risk of bleeding. Monitor pregnant women and neonates for any evidence of excessive bleeding.

Use in lactation

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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of Cablivi was evaluated in two placebo-controlled clinical studies (HERCULES, in which 71 patients received Cablivi; and TITAN, in which 35 patients received Cablivi). The data described below reflect exposure to Cablivi during the blinded periods of both studies, which include 106 patients with aTTP who received at least one dose, age 18 to 79 years, of whom 69% were female and 73% were Caucasian. The median treatment duration with Cablivi was 35 days (range 1-77 days).

The most frequent adverse reactions in clinical trials were epistaxis, headache and gingival bleeding. The most common serious adverse reaction was epistaxis.

Tabulated list of adverse reactions

Adverse reactions that occurred in $\geq 2\%$ of patients treated with Cablivi and more frequently than in those treated with placebo across the pooled data from the two trials are summarized in Table 1. Adverse reactions are also listed by MedDRA system organ class and by frequency. Frequencies are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Table 1 - Adverse Reactions in $\geq 2\%$ of patients treated with caplacizumab and more frequent than placebo during the blinded periods of the Phase II and III aTTP studies (Safety Population)

Adverse reaction	Caplacizumab (N=106) n (%)	Placebo (N=110) n (%)	Frequency category
<i>Gastrointestinal disorders</i>			
Gingival bleeding	17 (16)	3 (3)	Very common
Rectal haemorrhage	4 (4)	0 (0)	Common
Abdominal wall haematoma	3 (3)	1 (1)	Common
<i>General disorders and administration site conditions</i>			
Fatigue	16 (15)	10 (9)	Very common
Pyrexia	14 (13)	12 (11)	Very Common
Injection site haemorrhage	6 (6)	1 (1)	Common
Injection site pruritus	3 (3)	0 (0)	Common
<i>Musculoskeletal and connective tissue disorders</i>			
Myalgia	6 (6)	2 (2)	Common
<i>Nervous system disorders</i>			
Headache	22 (21)	15 (14)	Very common
<i>Renal and urinary disorders</i>			
Haematuria	4 (4)	3 (3)	Common
<i>Reproductive system and breast disorders</i>			
Vaginal haemorrhage	5 (5)	2 (2)	Common
Menorrhagia	4 (4)	1 (1)	Common
<i>Respiratory, thoracic and mediastinal disorders</i>			
Epistaxis	31 (29)	6 (6)	Very common

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Adverse reaction	Caplacizumab (N=106) n (%)	Placebo (N=110) n (%)	Frequency category
Dyspnoea	10 (9)	5 (5)	Common
<i>Skin and subcutaneous tissue disorders</i>			
Urticaria *	15 (14)	7 (6)	Very common

*Urticaria: was observed primarily during the plasma exchange period

One case of subarachnoid haemorrhage was observed in each study, which could have been related to TTP or treatment.

Description of selected adverse reactions

Bleeding

In clinical studies, bleeding events occurred in different body systems, independent of treatment duration. Although in some cases these events were serious and required medical attention, most were self-limited and all resolved. In case of active clinically significant bleeding, consider actions outlined in Section 4.4 and Section 4.9.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems (Australia).

4.9 OVERDOSE

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

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

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 trials

The efficacy and safety of caplacizumab in adults experiencing an episode of aTTP was established in a pivotal multicentre, randomised, double-blind, placebo-controlled trial ALX0681-C301 (HERCULES).

Efficacy

Study ALX0681-C301

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;

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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 1 - Changes in plasma exchange treatment and hospitalisations observed with caplacizumab in the HERCULES Study

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

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

Immunogenicity

In clinical studies, up to 9% 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

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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.

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5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been performed to evaluate the genotoxic potential of caplacizumab. As a large protein molecule, caplacizumab is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity studies have been conducted with caplacizumab. Based on findings from general toxicity studies with the drug in animals and considering its mechanism of action, no particular concern for carcinogenicity in patients treated with Cablivi is held.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder

Sucrose

Citric acid

Sodium citrate dihydrate

Polysorbate 80

Solvent

Water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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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.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Keep Cablivi in the refrigerator at 2°C to 8°C.

If necessary, Cablivi may be stored at room temperature up to 25°C for a single period of up to 2 months. Once the product has been taken out of the refrigerator the product should be discarded or used, but must not be returned to the refrigerator.

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 (polypropylene) 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

Any unused medicine should be disposed of by taking to your local pharmacy. The syringe and needle cap should be disposed of in a sharps container.

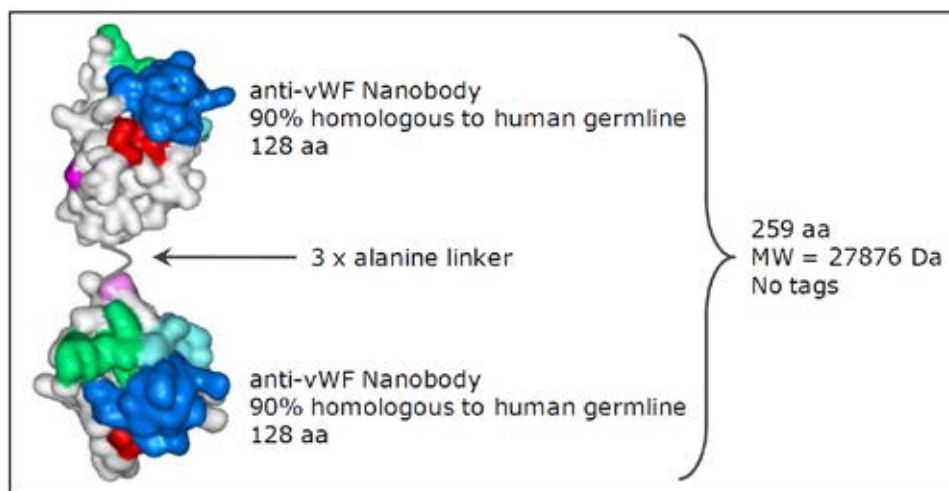
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

ALX-0081 is a sequence optimized bivalent Nanobody produced in *E. coli* that consists of two identical humanized building blocks (denominated PMP12A2h1) that are genetically linked by a tri-alanine linker.

ALX-0081 consists of 259 amino acids and has a molecular weight of 27876 Dalton. A schematic representation is shown in Figure 1.

Figure 1 - Schematic structure of ALX-0081



CDR-loops are coloured as follow: CDR1 in green, CDR2 in cyan and CDR3 in blue. Red and purple residues refer to hallmark residues which are different for a VHH compared to a human VH. CDR: Complementarity Determining Region

CAS number

915810-67-2

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7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

sanofi-aventis pty ltd

12-24 Talavera Road
Macquarie Park NSW 2113
Australia

Tel: 1800 818 806

9 DATE OF FIRST APPROVAL

05 February 2020

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information