30 April 2020
DOC_REF_ID
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cablivi

International non-proprietary name: caplacizumab

Procedure No. EMEA/H/C/004426/II/0021

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

aTTP..... acquired thrombotic thrombocytopenic purpura
AUCss..... steady-state area under the curve
BMI..... body mass index
CL..... clearance
CRCL ..... creatinine clearance
Css,max..... maximum concentration at steady-state
Css,min..... minimum concentration at steady-state
CV ..... coefficient of variation
DDT ..... data definition table
IIV ..... interindividual variability
NHANES..... National Health and Nutrition Examination Survey
PCI..... percutaneous coronary intervention
PD..... pharmacodynamic
PE ..... plasma exchange
PIP..... Agreed paediatric investigation plan
PK..... pharmacokinetic
PKPD ..... pharmacokinetic-pharmacodynamic
Q ..... inter-compartmental clearance
QD ..... once daily
RSE..... relative standard error
SC..... subcutaneous
SHR ..... shrinkage
TTP ..... thrombotic thrombocytopenic purpura
ULvWF ..... ultra-large multimers of von Willebrand factor
Vc..... central volume of distribution
Vp..... peripheral volume of distribution
vWF ..... von Willebrand factor
vWF:Ag ..... von Willebrand factor antigen
WT..... body weight

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Ablynx NV submitted to the European Medicines Agency on 28 November 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

The MAH initially submitted a C.I.4 variation to provide the results of the study ALX-0681-MS-01, a Modelling/Simulation study performed for the paediatric population as part of the approved Paediatric Investigation Plan (EMEA-001157-PIP-01-11-M02) for Cablivi.

During the evaluation of the variation, the application was upgraded to an extension of indication variation C.I.6.a to include adolescents in in the indication: treatment of patients experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression. Therefore, the scope has been amended as follows:

Extension of indication to include adolescents of 12 years of age and older weighing at least 40 kg in the authorised indication for Cablivi; as a consequence, sections 4.1, 4.2, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Information relating to orphan designation

Cablivi was designated as an orphan medicinal product EU/3/09/629 on 30 April 2009. Cablivi was designated as an orphan medicinal product in the following indication: treatment of thrombotic thrombocytopenic purpura.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0189/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0189/2016 was completed.

The PDCO issued an opinion on compliance for the PIP (EMEA-C-001157-PIP-01-11-M02).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	28 November 2019
Start of procedure:	30 December 2019
CHMP Rapporteur Assessment Report	3 February 2020
CHMP members comments	17 February 2020
Updated CHMP Rapporteur Assessment Report	20 February 2020
Request for supplementary information (RSI)	27 February 2020
CHMP Rapporteur Assessment Report	14 April 2020
CHMP members comments	20 April 2020
Updated CHMP Rapporteur Assessment Report	23 April 2020
CHMP Opinion	30 April 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Cablivi is currently indicated for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.

With this application, the indication now covers adolescents of 12 years of age and older weighing at least 40 kg as follows: "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."

The clinical presentation of aTTP during childhood is very similar to that of adults and similar to that of the initial presentation of congenital TTP.

Epidemiology, aetiology and pathogenesis

Acquired TTP is primarily a disease diagnosed in adults, although there are reports of cases in children. TTP is a rare and life-threatening disorder in which ultra large von Willebrand factor (ULvWF) has been implicated. It is characterised by microangiopathic haemolysis and platelet aggregation/hyaline thrombi whose formation is unrelated to coagulation system activity. Platelet microthrombi form in the microcirculation (i.e. arterioles, capillaries) throughout the body causing partial occlusion of vessels. Organ ischaemia, thrombocytopenia and erythrocyte fragmentation (schistocytes) occur.

From what is known about paediatric aTTP, the disease is similar in adults and paediatric patients, aTTP is more frequent in adolescents as compared to younger children. As in adults, aTTP in children and adolescents is most often associated with inhibitors of ADAMTS13. This is generally idiopathic, but may also be associated with other autoimmune disorders, in particular systemic lupus erythematosus.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

This variation concerns the submission of the results of the study ALX-0681-MS-01, a Modelling/Simulation study performed for the paediatric population and part of the agreed Paediatric Investigation Plan (EMEA-001157-PIP-01-11-M02) for Cablivi (caplacizumab), a nanobody indicated for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.

Based on the M/S results and the absence of clinical and safety data in children submitted, the MAH initially did not propose an update to the indication, but proposed to update the SmPC sections 4.2, 5.1 and 5.2 with regards to the paediatric population, including the results of all studies performed in compliance with the agreed PIP. The Paediatric Committee has issued a positive Opinion on compliance with the agreed PIP (EMEA-C-001157-PIP-01-11-M02). This variation application is also requesting the additional 2 years extended market exclusivity for Cablivi in accordance with Article 37 of Regulation (EC) No 1901/2006.

From what is known about paediatric aTTP, the disease is similar in adults and paediatric patients, and an unmet medical need could be foreseen also for the paediatric population, in particular for adolescents in whom aTTP is more frequent as compared to younger children. For children with a mature coagulation system, the efficacy and safety of caplacizumab is likely to be similar as in adults based on the mechanism of action of caplacizumab and the current knowledge of aTTP in the paediatric

population. The modelling/simulation data are deemed robust enough to support a posology in paediatric patients weighing over 40 kg.

Considering that the modelling study conducted was well performed and the suggested posology satisfactory based on the simulation results, this application was upgraded during the evaluation to an extension of indication to include adolescents with a body weight above 40 kg in the indication in the indication.

There are however no clinical data available in the paediatric population to support the simulated results. The phase II and III trials that preceded MA (ALX0681-2.1/10 (a therapeutic exploratory trial): open in 22 sites during the trial's last 1.25 years of recruitment and ALX0681-C301: open in 7 sites during the trial's last 0.25 years (3 months) were amended after most adult patients had been recruited and opened for paediatric subjects, but none were recruited. The CHMP does not consider that additional clinical data are needed to include adolescents in the indication.

2.3.2. PK/PD modelling

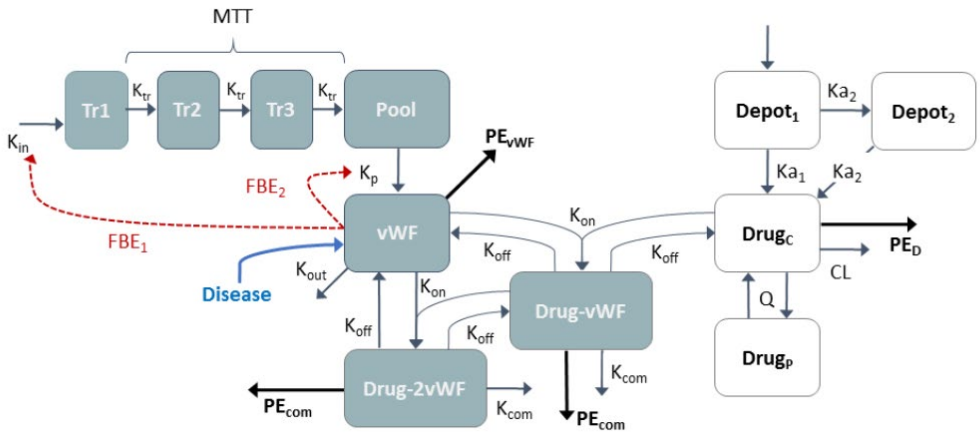
Objective

Perform a Modelling and Simulation study to propose appropriate posology in the paediatric population 2-17 years old.

Methods – analysis of data submitted

Population PKPD model

A PKPD model has previously been developed on adult data (see figure below). The MAH has used the PKPD model to simulate out appropriate posology in paediatric population. The population PK/PD model, characterising the relationship between drug exposure and the pharmacodynamics effect (in terms of total vWF levels), was built using nonlinear mixed-effects modelling. Data was included from Study 1 (ALX-0081/0681-01/06), Study 2 (ALX-0081/0681-1.2/08a) and Study 3 (ALX-0081/0681-1.2/08b), Study 4 (ALX-0081/0681-1.2/08c OLE), Study 5 (ALX-0081/0681-1.1/08 First part) and Study 6 (ALX-0081/0681-1.1/08 Second part), Study 7 (ALX-0081/0681-2.1/09), Study 8 (ALX-0681-2.1/10), Study 9 (ALX-0681-C102) and Study 10 (ALX-0681-C301).



The model components are described below:

Depot1: depot compartment s.c dosing, Depot2: delayed absorption compartment following s.c dosing, DrugC: free drug compartment, DrugP: peripheral drug compartment, Drug-vWF: dimer (drug-vWF) complex, Drug-2VWF: trimer (drug-vWF-drug) complex, Tr1, Tr2, Tr3: vWF precursor transit compartment, MTT: mean transit time, Pool: vWF precursor pool, vWF: free vWF, Ka1: first-order (fast) absorption rate for s.c dosing, Ka2: first-order (slow) absorption rate for s.c dosing, CL: drug non-target mediated clearance, Q: drug inter-compartmental clearance, PED: PE mediated drug elimination rate, Kon: association rate constant, Koff: dissociation rate constant, Kcom: complex elimination rate, PEcom: PE mediated complex elimination rate, Kout: elimination rate of free vWF, PEvWF: PE mediated free vWF elimination rate, Kin: production rate for vWF, Ktr: transit rate constant, Kp: pool transfer rate, FBE1: feedback effect parameter 1, FBE2: feedback effect parameter 2, Disease: disease effect on baseline free vWF Total vWF = free vWF + vWF bound in dimer complex + 2 x vWF bound in trimer complex. Total drug = free drug/Vc +drug bound in dimer complex + drug bound in trimer complex.

Caplacizumab is subject to target-mediated drug disposition meaning that its pharmacokinetics (PK) is influenced by the pharmacodynamics (PD).

Simulation assumptions for paediatric population

The main assumptions in the simulations were:

- Expression of vWF in diseased children is similar to diseased adults.
- Similar affinity of caplacizumab to the vWF target as in adults
- Similar body composition to normal US children, the dependence of body weight on gender and age in the selected population of juvenile patients is reasonably approximated by the NHANES database from the National Centre of Health Statistics
- The body weight distribution in adult population was assumed to be similar to the studied aTTP adult population in Study 8 (ALX0681-2.1/10, TITAN) and Study 10 (ALX0681-C301, HERCULES) with a median of 80 kg (minimum 46.5 kg and maximum 150 kg)
- The gender proportion among paediatric thrombotic thrombocytopenic purpura (TTP) patients is the same as in adults (approximately 1/3 males and 2/3 females)
- To capture the CRCL covariate effect on CL, the CRCL values in the paediatric population were allometrically scaled to adults with an assumed normal renal function for a 70 kg subject of 120 ml/min.
- The typical CL, Q, Vc and Vp in paediatrics were assumed to be allometrically scaled to adults.

Results

PK simulations

Flat-dose

To illustrate the need for a weight-based dosing regimen in paediatric patients, the population predictions of the caplacizumab exposure (AUCss) following a flat dose of 10 mg once daily SC caplacizumab during forty days are presented in the figure below for the different age categories (adults based on PK observed in clinical trials). AUC increases in the younger patients (due to lower body weight).

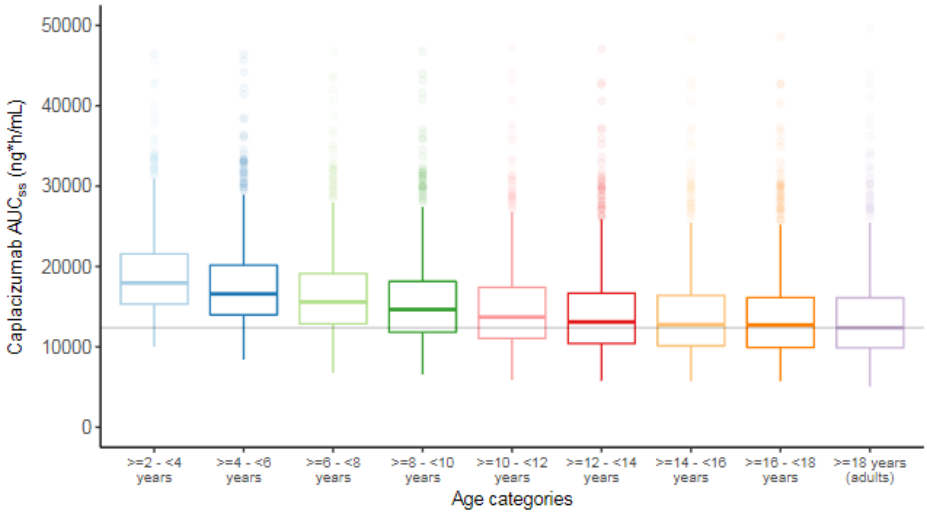


Figure 6: Box-plots of caplacizumab AUC_{ss} for the different age categories, following daily SC flat dosing of 10 mg caplacizumab for forty days, including an IV loading dose of similar strength, 1 hour PE treatment during the first seven days and disease progression in vWF:Ag. The horizontal colored lines indicate the median AUC_{ss}, the boxes indicate the 25^{th} and 75^{th} percentiles, and the upper/lower whiskers extend from the box to the largest/smallest value no further than 1.5 * IQR (inter-quartile range) from the box. The horizontal grey line indicates the median AUC_{ss} in the adult population for ease of comparison. Emphasis on outlying values (i.e. higher or lower than the whisker) were toned down.

Proposed weight-based dosing

The exposure predictions using weight-based dosing are shown in figures and table below (adults based on PK observed in clinical trials). The setup was daily SC dosing for forty days of 5 mg caplacizumab for paediatric patients with body weight<40 kg and 10 mg caplacizumab for paediatric patients with body weights above 40 kg or adults.

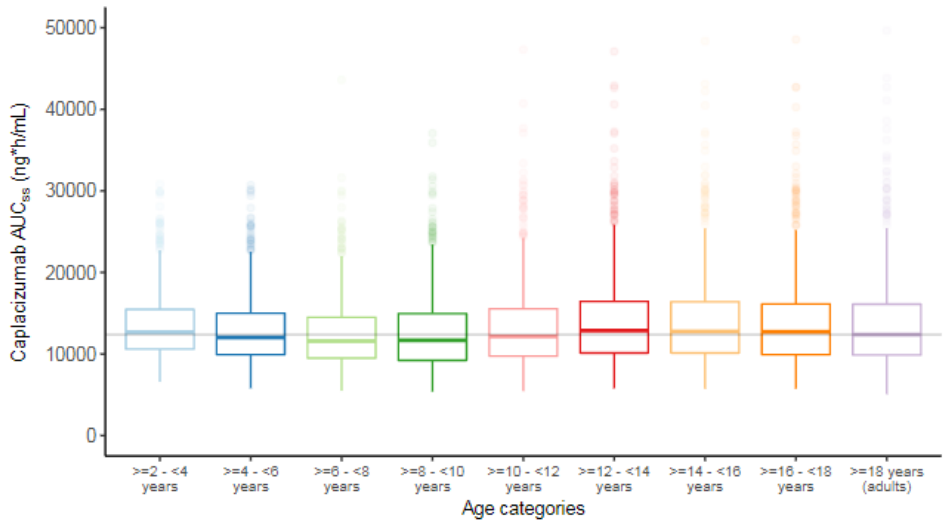


Figure 9: Box-plots of caplacizumab AUC_{ss} for the different age categories, following daily SC weight based dosing for forty days of 5 mg caplacizumab for pediatric patients with body weight <40 kg and 10 mg caplacizumab for pediatric patients with body weights ≥40 kg or adults, including an IV loading dose of similar strength, 1 hour PE treatment during the first seven days and disease progression in vWF:Ag. The horizontal colored lines indicate the median AUC_{ss}, the boxes indicate the 25^{th} and 75^{th} percentiles, and the upper/lower whiskers extend from the box to the largest/smallest value no further than 1.5 * IQR (inter-quartile range) from the box. The horizontal grey line indicates the median AUC_{ss} in the adult population for ease of comparison. Emphasis on outlying values (i.e. higher or lower than the whisker) were toned down.

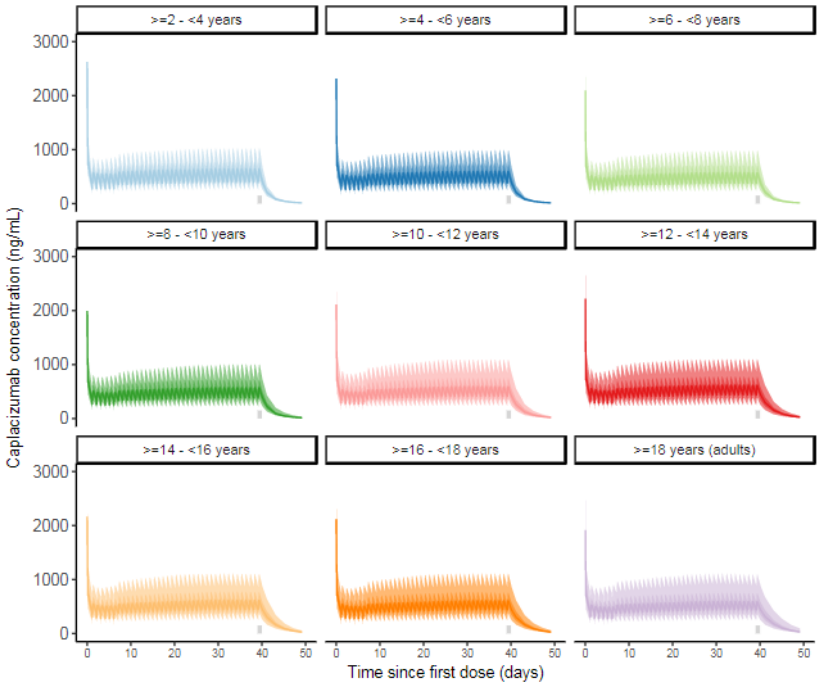


Figure 7: Simulated caplacizumab population concentration time-course for different age categories, following daily SC weight based dosing for forty days of 5 mg caplacizumab for pediatric patients with body weight <40 kg and 10 mg caplacizumab for pediatric patients with body weights ≥40 kg or adults, including an IV loading dose of similar strength, 1 hour PE treatment during the first seven days and disease progression in vWF:Ag. The line indicates the simulated median, and the shaded areas indicate the 50 and 90% prediction intervals of the simulated values. The grey shaded areas indicate the point in time where the AUC_{ss}, $C_{ss,max}$ and $C_{ss,min}$ was derived.

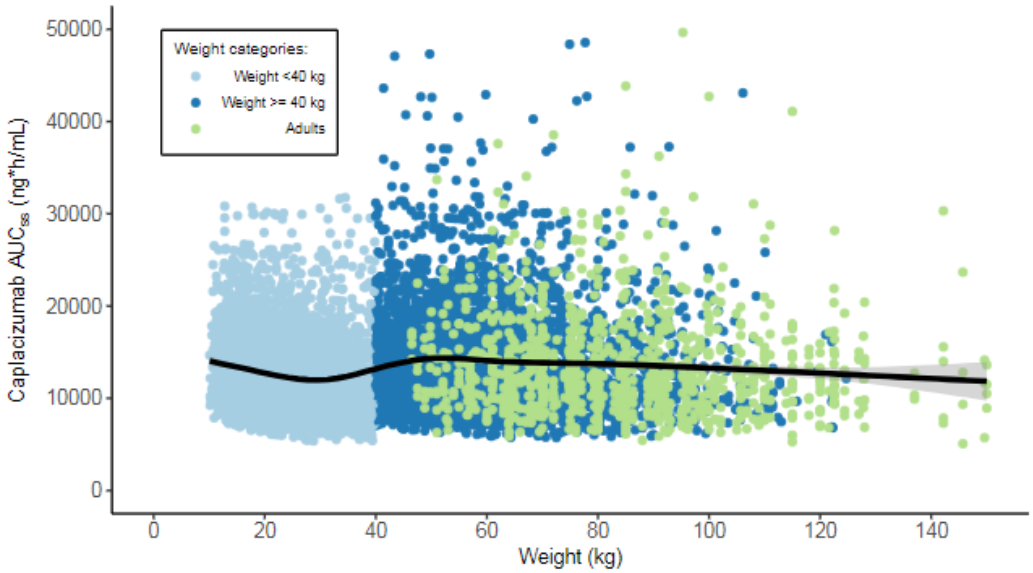


Figure 12: Relationship between simulated caplacizumab AUC_{ss} and body weight following daily SC weight based dosing for forty days of 5 mg caplacizumab for pediatric patients with body weight <40 kg and 10 mg caplacizumab for pediatric patients with body weights ≥40 kg or adults, including an IV loading dose of similar strength, 1 hour PE treatment during the first seven days and disease progression in vWF:Ag. The black line is a smooth indicating the trend, with each color indicating a body weight category as indicated in the legend.

Table 7: Overview of the AUC_{ss}, $C_{ss,max}$ and $C_{ss,min}$ by age category for the corresponding caplacizumab dose on day forty, following QD SC weight based dosing of 5 mg caplacizumab for pediatric patients with body weight <40 kg and 10 mg caplacizumab for pediatric patients with body weights ≥40 kg or adults, for the median, 5th and 95th percentiles (prc.).

Age range	AUC_{ss} (ng*h/mL)			$C_{ss,max}$ (ng/mL)			$C_{ss,min}$ (ng/mL)		
(years)	Median	5th prc.	95th prc.	Median	5th prc.	95th prc.	Median	5th prc.	95th prc.
≥2 - <4	12685	8462	20935	656.5	443.6	1035.4	390.4	256.9	665.3
≥4 - <6	12029	7832	20521	613.0	408.0	1004.0	381.2	239.1	663.8
≥6 - <8	11584	7435	20382	587.2	379.0	990.0	372.4	231.3	670.8
≥8 - <10	11680	7068	21189	587.9	368.3	1028.0	384.3	222.3	716.5
≥10 - <12	12158	7303	23479	608.8	374.5	1105.0	410.5	232.5	833.0
≥12 - <14	12869	7706	23726	628.3	396.6	1152.2	436.4	244.8	862.9
≥14 - <16	12762	7753	24028	629.2	398.3	1139.0	437.2	250.3	860.3
≥16 - <18	12723	7555	24113	622.5	388.3	1121.4	434.1	242.9	861.1
≥18 (adults)	12381	7295	23794	608.8	371.8	1123.7	435.3	242.1	873.4

PD simulations

The median vWF:Ag population time-courses predicted for each of the paediatric age categories and adults are presented in the Figure below. As expected, with similar exposure in all age groups and assuming a similar PD model, the median vWF:Ag is expected similar between all age groups.

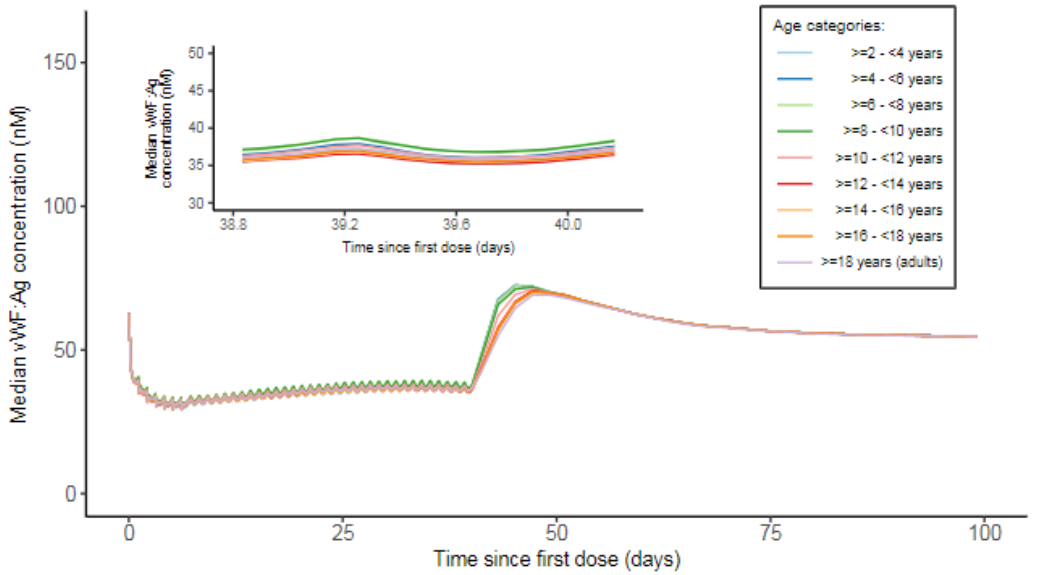


Figure 17: Simulated median absolute vWF:Ag time-course for different age categories, following daily SC weight-based dosing for forty days of 5 mg caplacizumab for pediatric patients with body weight <40 kg and 10 mg caplacizumab for pediatric patients with body weights ≥40 kg or adults, including an IV loading dose of similar strength, 1 hour PE treatment during the first seven days and disease progression in vWF:Ag, with a zoom on the concentration time-course during the last dosing interval. The colors correspond to age categories as indicated in the legend.

2.3.3. Discussion on clinical pharmacology

PKPD modelling

The developed PKPD model for adults has previously been assessed and deemed adequate for describing the adult data and performing simulations within the studied range of doses, treatment period, covariate values. The adult model included allometric scaling with fixed exponents and

assuming allometric scaling with fixed exponents in children is considered acceptable and the model is deemed adequate for simulations in paediatric patients down to 2 years old. Gender, BMI and age are not included in the model.

Simulation results

The simulations for the flat-dose and weight-based dosing illustrate and support that lowering the dose to 5 mg in patients under 40 kg is appropriate.

Overall the modelling conducted is well performed and the suggested posology satisfactory based on the simulation results. There are however no clinical data submitted in the paediatric population to support the simulated results.

Clinical aspects

The applicant has assumed similar disease in children as in adults which is considered reasonable, based on what is described in literature about aTTP in the paediatric population, occurring less frequently but with similar clinical features as in the adult population.

Based on the mechanism of action of caplacizumab, and the similar pathogenesis of aTTP in children as compared to adults, efficacy of caplacizumab could be expected to be similar as in adults.

In this situation, a PK-based extrapolation of efficacy from adults could have been sufficient, however, no PK data are available, and it is uncertain whether it could be feasible to collect such data in the future. However in paediatric patients the simulations for the flat-dose and weight-based dosing illustrate and support that lowering the dose to 5 mg in paediatric patients weighing less than 40 kg is appropriate.

For safety, administration of caplacizumab in adults has been associated with primarily mucosal bleeding. It is not foreseen that the risk of using caplacizumab in the paediatric population with a mature coagulation system would differ significantly from what is seen in adults.

For the youngest children, with a less mature coagulation system, the risk of using caplacizumab could be different and cannot be assessed without clinical data.

2.3.4. Conclusions on clinical pharmacology

The MAH has completed the PIP for Cablivi and provided results from a modelling/simulation study performed for the paediatric population. No clinical data for the paediatric population have been collected despite efforts made by the MAH to include children in the phase II and III trials that preceded marketing authorisation. Overall the modelling conducted is well performed and the suggested posology satisfactory based on the simulation results. There are however no clinical data available in the paediatric population to support the simulated results.

From what is known about paediatric aTTP, the disease is similar in adults and paediatric patients, and an unmet medical need could be foreseen also for the paediatric population, in particular for adolescents in whom aTTP is more frequent as compared to younger children. In post-pubertal children, the coagulation system is considered to be mature. The efficacy and safety of caplacizumab is likely to be similar as in adults based on the mechanism of action of caplacizumab and the current knowledge of aTTP in the paediatric population. The modelling/simulation data are deemed robust enough to support a posology in paediatric patients weighing over 40 kg.

An additional 2 years extended market exclusivity for Cablivi in accordance with Article 37 of Regulation (EC) No 1901/2006 is deemed appropriate.

2.3.5. PSUR cycle

The requirements for submission of periodic safety update reports 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.

2.4. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI (section 4.4 of the SmPC) to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s).

2.4.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cablivi is currently indicated for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.

With this application, the indication now covers adolescents of 12 years of age and older weighing at least 40 kg as follows: "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."

3.1.2. Balance of benefits and risks

The developed PKPD model for adults has previously been assessed and deemed adequate for describing the adult data and performing simulations within the studied range of doses, treatment period, covariate values. The adult model included allometric scaling with fixed exponents and assuming allometric scaling with fixed exponents in children is considered acceptable, the model is deemed adequate for simulations in paediatric patients down to 2 years old. Gender, BMI and age are not included in the model.

The simulations for the flat-dose and weight-based dosing illustrate and support that lowering the dose to 5 mg in patients under 40 kg is appropriate.

Overall the modelling conducted is well performed and the suggested posology satisfactory based on the simulation results.

No clinical data for the paediatric population have been collected despite attempts made by the MAH to include children in the phase II and III trials that preceded marketing authorisation. However, from what is known about paediatric aTTP, the disease is similar in adults and paediatric patients, and an unmet medical need could be foreseen also for the paediatric population, in particular for adolescents in whom aTTP is more frequent as compared to younger children. For children with a mature coagulation system, the efficacy and safety of caplacizumab is likely to be similar as in adults based on the mechanism of action of caplacizumab and the current knowledge of aTTP and its response to intervention (such as plasma exchange) in the paediatric population. The modelling/simulation data are deemed robust enough to support a posology in paediatric patients weighing over 40 kg.

For safety, administration of caplacizumab in adults has been associated with primarily mucosal bleeding. It is not foreseen that the risk of using caplacizumab in the paediatric population with a mature coagulation system would differ significantly from the risk in adults.

3.2. Conclusions

The overall B/R of Cablivi in the treatment of 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 is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

The MAH initially submitted a C.I.4 variation to provide the results of the study ALX-0681-MS-01, a Modelling/Simulation study performed for the paediatric population as part of the approved Paediatric Investigation Plan (EMEA-001157-PIP-01-11-M02) for Cablivi.

During the evaluation of the variation, the application was upgraded to an extension of indication variation C.I.6.a to include adolescents weighing over 40 kg in in the indication: treatment of patients experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression. Therefore, the scope has been amended as follows:

Extension of indication to include adolescents weighing over 40 kg in the authorised indication for Cablivi; as a consequence, sections 4.1, 4.2, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Conditions or restrictions with regards 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.

In addition, 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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0189/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0021'