Date: 17 May 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Evusheld

International non-proprietary name: cilgavimab / tixagevimab

Pharmaceutical form: solution for injection

Dosage strength(s): 150 mg/1.5 mL + 150 mg/1.5 mL

Route(s) of administration: intramuscular

Marketing Authorisation Holder: AstraZeneca AG

Marketing Authorisation No.: 68704

Decision and Decision date: temporary authorisation in accordance with Art. 9a TPA approved on 9 September 2022

Note:

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

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.

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1 Terms, Definitions, Abbreviations

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ESRD	End-stage renal disease
FAS	Full pre-exposure analysis set
Fc	Fraction crystallisable
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
i.m.	Intramuscular
INN	International nonproprietary name
IMP	Investigational medicinal product
ITT	Intention-to-treat
i.v.	Intravenous
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
nAb	Neutralising antibody
NLF	Nasal lining fluid
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetic
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
RRR	Relative risk reduction
RT-PCR	Reverse transcription polymerase chain reaction (test)

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SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
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)
UGT	Uridine 5'-Diphospho-Glucuronosyltransferase
VOC	Variants of concern
WCB	Working cell bank

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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 substances cilgavimab and tixagevimab of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Evusheld (tixagevimab and cilgavimab) is indicated for the prophylaxis of COVID-19 in adults and paediatric individuals (12 years of age and older weighing at least 40 kg) (see "Dosage/Administration" and "Pharmacokinetics").

2.2.2 Approved Indication

Evusheld (tixagevimab and cilgavimab) is indicated for pre-exposure prophylaxis of COVID-19 in adults and adolescents (12 years of age and older weighing at least 40 kg):

- unable to produce an adequate immune response to the SARS-CoV-2 vaccine

and

- who are not currently infected with SARS-CoV-2 and who have not had recent contact with a person infected with SARS-CoV-2.

See "Dosage/Administration" and "Pharmacokinetics".

Evusheld is not approved for the treatment or post-exposure prophylaxis of COVID-19.
Evusheld is not intended as a substitute for vaccination against COVID-19.
Evusheld should be used according to official recommendations.

Decisions regarding the use of Evusheld for pre-exposure prophylaxis should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viruses, including regional or geographic differences, as well as available information about susceptibility to Evusheld (see "Properties/Effects").

2.2.3 Requested Dosage

Summary of the applied standard dosage:

The recommended dosage is 300 mg of Evusheld administered as two separate consecutive intramuscular injections of 1.5 ml each:
• 150 mg of tixagevimab
• 150 mg of cilgavimab

A singular intramuscular administration in the PROVENT study showed efficacy for a minimum of 6 months (see "Pharmacokinetics"). There are no data available with repeat dosing.

Paediatric population
The safety and efficacy of Evusheld have not been shown in children younger than 18 years of age. No data are available.
It is expected that the recommended dosage in persons of 12 years of age and older weighing at least 40 kg show serum exposures of tixagevimab and cilgavimab comparable with those observed in adults, as adults with a similar body weight were included in the clinical studies PROVENT and STORM CHASER (see "Properties/Effects - Pharmacodynamics" and "Pharmacokinetics").

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Mode of administration
Evusheld is intended for intramuscular (i.m.) use only.
Tixagevimab and cilgavimab should be administered as two separate consecutive intramuscular injections into different injection sites, preferably one injection per gluteal muscle.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	09 February 2022
Formal control completed	10 February 2022
List of Questions (LoQ)	25 May 2022
Answers to LoQ	24 June 2022
Predecision	22 July 2022 and 29 July 2022
Answers to Labelling corrections	22 August 2022
Final Decision	09 September 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Coronavirus Disease 2019 (COVID-19) is a pandemic disease that started in Wuhan, China, in December 2019. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The COVID-19 clinical spectrum ranges from asymptomatic infection to severe disease. The majority of patients will present non-severe (flu-like syndrome) or mild symptoms (mild pneumonia). However, up to 20% of patients will present severe (important lung involvement leading to impairment of gas exchange function) or critical disease (including respiratory failure, thrombosis, multiorgan dysfunction) that might ultimately lead to death. Patients with risk factors (e.g. old age, obesity, chronic lung, kidney or heart disease, active cancer or immunosuppression, diabetes) are especially at higher risk of a severe course and death.

Vaccines based on various technologies have been developed for the prevention of COVID-19 and are widely used in Switzerland. Some vulnerable patients might be unable to mount an adequate antibody response after vaccination (e.g. immunocompromised patients) or present contraindications to vaccination. The use of monoclonal antibodies as pre-exposure prophylaxis might be a useful addition to the COVID-19 therapeutics arsenal. So far, in Switzerland, the monoclonal antibody combination casirivimab/imdevimab has been approved for this pre-exposure indication.

Evusheld consists of a combination of two recombinant human IgG1κ monoclonal antibodies, tixagevimab and cilgavimab, that simultaneously bind to non-overlapping regions of the spike protein receptor binding domain of SARS-CoV-2, thereby blocking its interaction with the human ACE2 receptor, resulting in a blockade of virus entry. The half-lives of these monoclonal antibodies have been extended (to 90 days) by introducing YTE (M252Y/S254T/T256E, resulting in a 10-fold slower dissociation rate of Fc and FcRn and an extended half-life) and TM (L234F/L235E/P331S, resulting in decreased binding to FcRI, II, III and C1q and decreased complement-dependent cytotoxicity) substitutions in the Fc part.

4 Quality Aspects

4.1 Drug Substance

Evusheld is a combination of two severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific antiviral IgG1 monoclonal antibodies (cilgavimab and tixagevimab) that bind to non-overlapping epitopes on the receptor binding domain of the spike protein and block its interaction with the human angiotensin-converting enzyme 2 host cellular receptor, resulting in a blockade of virus entry, effectively neutralising the SARS-CoV-2 virus.

Since effector function via the Fc domain is not considered part of the mode of action, amino acid substitutions that reduce binding to Fc gamma receptors and to C1q were introduced into both antibodies. In addition, amino acid substitutions that extend the half-life by enhancing affinity to the neonatal Fc receptor were introduced into both antibodies.

Cilgavimab (AZD1061) is a monoclonal antibody (molecular weight approx. 152,000 Da) composed of two heavy chains consisting of 461 amino acid residues each and two light chains consisting of 219 amino acid residues each.

Tixagevimab (AZD8895) is a monoclonal antibody (molecular weight approx. 149,000 Da) composed of two heavy chains consisting of 453 amino acid residues each and two light chains consisting of 216 amino acid residues each.

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Each antibody carries one primarily N-linked biantennary complex-type glycans attached to each heavy chain.

The cilgavimab and tixagevimab drug substances are each produced separately in Chinese hamster ovary (CHO) cells. For each antibody, a two-tiered cell banking system of master cell bank (MCB) and working cell bank (WCB) is in place. After thawing of the respective WCB vial, the cells are grown in suspension culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The culture is harvested, and purification is performed with a series of chromatography steps, ultra-/diafiltration steps, and viral inactivation and viral filtration steps. The two antibodies are formulated separately with the excipients.

The cilgavimab and tixagevimab drug substances are each produced at two different manufacturing sites. The manufacturing processes for the two drug substances have been validated at each site with multiple sequential batches; the data demonstrated a consistent production and an efficient removal of impurities.

Several changes were implemented during the development of the cilgavimab and tixagevimab drug substance manufacturing processes, including changes to manufacturing site and production scale. However, the analytical comparability studies, which included batch release data, extended characterisation data, and forced degradation studies, demonstrated comparability between the different processes and sites, respectively.

The characterisation of the physicochemical and biological properties of the cilgavimab and tixagevimab drug substances and their impurities was performed using state-of-the-art methods.

The specifications for cilgavimab and tixagevimab drug substance release and stability include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on clinical experience, batch analysis data, stability data, platform knowledge, and are in conformance with compendial or regulatory guidelines.

Batch analysis data for clinical batches, and commercial batches of cilgavimab and tixagevimab drug substance were provided; all batch release data comply with the drug substance specifications that were valid at the time of batch release. All specific analytical methods are described and are fully validated.

The cilgavimab and tixagevimab drug substances are stored at 2 - 8°C.

4.2 Drug Product

Evusheld, solution for injection, is supplied as a combination pack consisting of two borosilicate glass vials, i.e. one vial containing formulated cilgavimab (150 mg or 100 mg/mL) and one vial containing formulated tixagevimab (150 mg or 100 mg/mL).
The drug product cilgavimab contains 100 mg/mL of cilgavimab L-histidine/L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, and water for injection.
The drug product tixagevimab contains 100 mg/mL of tixagevimab L-histidine/L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, and water for injection.

The two formulations (cilgavimab, tixagevimab) do not contain antimicrobial preservatives.
During process development of the two drug products, additional manufacturing sites were implemented. However, comprehensive characterisation studies, release data, and forced degradation studies demonstrated comparability between the different processes.

The glass vials and stoppers for the drug products meet compendial requirements.

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The cilgavimab and tixagevimab drug products are manufactured separately. The drug product manufacturing processes consist of warming of the respective formulated drug substance, pooling and mixing, sterile filtration and aseptic filling at the respective target fill volume, capping, visual inspection, labelling, and secondary packaging.

The drug product manufacturing processes for cilgavimab and tixagevimab were validated with several consecutive batches; the data demonstrated a consistent production.

The specifications for release and stability of the drug products include relevant tests and acceptance criteria, e.g. for identity, purity, quantity, potency, appearance, pH, osmolality, visible and sub-visible particles, bacterial endotoxins, and sterility. The drug product specifications comply with compendial or regulatory guidelines.

Batch analysis data for several batches of the two drug products, including clinical batches, and commercial batches, were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release. All specific analytical methods are validated.

The vials are stored at 2 – 8°C protected from light. A shelf life of 18 months for both drug products was granted. Each carton of finished goods contains one vial each of cilgavimab and tixagevimab finished product.

4.3 Quality Conclusions

Satisfactory and consistent quality of the cilgavimab and tixagevimab drug substances and drug products has been demonstrated. Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Evusheld, Swissmedic conducted an abridged evaluation, which was based on the EMA assessment report (24.03.2022) provided by the applicant. Swissmedic's nonclinical evaluation focused on the PD data, viral resistance and neutralisation activities against mutants; especially currently circulating Omicron variants.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Evusheld in the proposed indication.
Evusheld binds to the non-overlapping epitopes of S-protein with high affinity. It does not show any Fc function.
Neutralisation assays showed that Evusheld retains its activity against all tested variants except for Omicron variants BA.1.0 and BA.1.1 (up to 424-fold reduced activity).
Based on a summary of studies with other Omicron variants, which was provided by the applicant in response to a respective stipulation, Evusheld remained active against Omicron variants BA.2 and BA.2.12.1 in studies using pseudovirus. However, slightly reduced activity was observed against BA.3 (16-fold), and a marked reduction in activity was measured against the BA.4/5 variants (up to 65-fold).The applicant will be requested to submit the study reports including the results with authentic virus (post-approval requirement).
The prophylactic activity of Evusheld is supported by the results from animal studies. Prophylactic administration to rhesus and cynomolgus macaques reduced viral subgenomic mRNA levels to levels below detection in nasal swab samples, indicating that Evusheld can prevent or reduce SARS-CoV-2 infection in the upper respiratory tract. Studies of SARS-CoV-2 transmission were not conducted.
The pharmaco-toxicological profile has been sufficiently characterised. There were no particular safety issues identified in the nonclinical studies that would be of concern for human use. The safety margins are considered sufficient. In line with ICH S6 (R1), carcinogenicity, genotoxicity, and reproductive toxicology studies were not conducted given that Evusheld is directed against an exogenous target.
The Nonclinical Safety Specifications in the RMP adequately address the nonclinical findings and their relevance for clinical use. All nonclinical data that are relevant for safety are also adequately mentioned in the information for healthcare professionals. There is no risk for the environment due to the protein nature of Evusheld.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

For the clinical pharmacology and clinical assessment, the EMA CHMP assessment report (EMA/CHMP/158104/2022) was also considered.

For the evaluation of the clinical and clinical pharmacology data of this application, previous regulatory decisions by the EMA or FDA were taken into account. In part, the available assessment reports and respective product information from the EMA or FDA were used as a basis for the clinical and clinical pharmacology evaluation. The evaluation focused on the aspects summarised below.

ADME
The PK of tixagevimab and cilgavimab was characterised for both antibodies individually and for the total antibody over a dose range of 150 – 1500 mg i.v., or at 150 mg i.m. for each antibody.

Absorption
After a single 300 mg i.m. dose (150 mg tixagevimab + 150 mg cilgavimab), C_{max} was reached after a median time of 14 days for both antibodies. The bioavailabilities were 69% and 65% for tixagevimab and cilgavimab, respectively.

Dose Proportionality
C_{max} and AUC of both antibodies increased linearly with increasing i.v. dose over the investigated dose range.

Pharmacokinetics after multiple Dosing
Only single doses have been administered to humans so far.

Distribution
After i.v. administration, the tixagevimab volume of distribution ranged from 5.1 to 6.5 L, and the cilgavimab volume of distribution ranged from 5.7 to 6.3 L in the investigated dose range.
Both antibodies distributed into the upper respiratory tract. At a dose of 300 mg i.m., the median partition coefficient of total antibody from serum to nasal lining fluid (NLF) was 1.81%. However, partition coefficients between subjects were very variable, and the concentration in NLF has been measured only with a qualified, but not validated, assay. Therefore, these data are considered as supportive only.
Distribution into lung tissue has not been investigated

Metabolism
No studies investigating the metabolism of tixagevimab or cilgavimab have been conducted considering the biological nature of the molecule.

Elimination
The tixagevimab clearance (CL) ranged from ~0.041 to 0.051 L/day, and cilgavimab CL ranged from ~0.046 to 0.052 L/day in the investigated dose range.
The terminal half-lives of tixagevimab and cilgavimab were similar across dose levels and for i.m. versus i.v. administration. The median half-lives were 89 and 84 days for tixagevimab and cilgavimab, respectively. The long half-life of both antibodies is due to modifications in the Fc regions.

Special Populations / Intrinsic Factors
The effect of demographic and disease-related factors on the PK of tixagevimab and cilgavimab was investigated in a PopPK analysis.

The final model for tixagevimab, cilgavimab, and total antibody following i.v. and i.m. administration was a two-compartment model with first-order absorption, first-order elimination and a combined proportional and additive error model.

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Body weight was included as a covariate on the volume and clearance parameters with fixed allometric scaling. In addition, statistically significant covariate effects were identified for sex, age and diabetes. However, the effects of these covariates on the total antibody exposure were limited and are not considered clinically relevant.

Hepatic impairment
The majority of the patients (97.1%) had normal hepatic function. 2.9 % of the patients had mild hepatic impairment, and no patients had moderate or severe hepatic impairment. Based on the available data, no dose adjustment is necessary for patients with mild hepatic impairment. Considering the biological nature of tixagevimab and cilgavimab, no relevant effects of moderate or severe hepatic impairment on the exposure of both antibodies are expected.

Renal impairment
The majority of patients (54.2%) had normal renal function. The dataset included 38.2% of patients with mild renal impairment, 6.8% of patients with moderate renal impairment, 10 patients (0.4%) with severe renal impairment and 11 patients (0.4%) with end-stage renal disease (ESRD). Renal function was not found to have a significant effect on tixagevimab or cilgavimab PK parameters. No dose adjustment is required for patients with impaired renal function.

A potential effect of anti-drug antibody (ADA) status on the PK was not assessed, as none of the subjects / patients was ADA positive. This may be related to the single dose administration and/or a limited drug tolerance of the ADA assay.

Effect of body weight and paediatric extrapolation for adolescents (age 12 - < 18 years and body weight of > 40 kg)
The PK of tixagevimab and cilgavimab has not been studied in patients <18 years of age. However, the overall weight range in the available PK dataset was 36 - 177 kg. Thus, the weight range relevant for an adolescent population was covered.
The expected exposure in adolescents was assessed using PopPK model-based simulations. These simulations indicated that the dose established for adults is expected to result in exposures in adolescents (>40 kg and >12 years of age) which are comparable to the exposure in adults.
This extrapolation approach is based on the assumption that potential differences in the PK between adolescents and adults are solely caused by differences in weight and no other age/maturation-dependent processes. Considering the comparatively uncomplicated PK of tixagevimab and cilgavimab (linear with respect to time and dose), and since the other significant covariates in the PopPK analysis are considered not to have clinically relevant effects on the exposure, this assumption is considered acceptable.

Interactions
No *in vitro* or clinical interaction studies were conducted. However, an effect of tixagevimab or cilgavimab on CYPs, UGTs or transporters via their metabolism, chemical properties or mechanism of action appears unlikely.

6.2 Dose Finding and Dose Recommendation

No specific dose-finding study was performed. A phase I study was designed to evaluate the safety, tolerability, and pharmacokinetics of Evusheld in healthy adult participants between 18 and 55 years of age. Dose levels (300 mg i.m. to 3000 mg i.v.) were selected based on available in vitro functional potency data and PK data.

The currently proposed 300 mg dosing was chosen based on (i) the in vitro IC_{50} of Evusheld for neutralisation of the original SARS-CoV-2 strain of approx. 10 ng/mL in microneutralisation assays, (ii) PK and neutralising antibody (nAb) titre results showing that it produced serum plaque reduction neutralising titre-80 (PRNT80) levels ranging from >256 to <1024, (iii) median serum to nasal lining

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fluid ratio of 1.81% as calculated in the Phase I study and (iv) a viral dynamic model indicating that 80% or more of virus entry inhibition is sufficient to prevent or accelerate eradication of infection.

Altogether, this implied that, systemically, the resulting inhibition by a 300 mg i.m. dose is higher than 80% with a 220-fold ratio over the IC_{50} of 10 ng/mL (2.2 µg/mL/0.010 µg/mL), which translates into >99.5% inhibition. A population PK model then predicted that the serum Evusheld concentration would remain above the minimum protective concentration of 2.2 µg/mL for at least 6 months.

The Omicron variants of concern (VOC), depending on the subvariants (i.e. BA.1, BA1.1, BA.2) and the assay methodology, exhibit IC_{50} values for the neutralisation by Evusheld ranging from 9.8 to 1147 ng/mL. For the Omicron VOC this indicates a 3.2- to 424-fold reduction in activity compared with the original SARS-CoV-2 strain. Importantly, this reduction in activity is especially relevant for the BA.1 and BA.1.1 subvariants, whereas Evusheld activity is less affected by the BA.2 subvariant (approx. 5 fold reduction against the wild-type). Based on PK/PD and viral dynamic modelling, the applicant is of the opinion that the potency loss of Evusheld does not imply that its duration of protection against symptomatic COVID-19 or upper respiratory tract infections for any Omicron subvariant will be shorter. No clinical data are currently available to support the claim that the single dose 300 mg regimen is insufficient, or whether higher dosage regimens or more frequent dosing should be used. Of note, in vitro data indicate that the IC_{50} of Evusheld against the recently emerging Omicron BA.4 and BA.5 subvariants is approx. 65 ng/mL, representing a 33- to 65-fold reduction in neutralising activity in pseudovirus assays.

6.3 Efficacy

Two Phase III pivotal studies examined the role of a 300 mg (150 mg of tixagevimab plus 150 mg of cilgavimab) intramuscular dose of Evusheld in the setting of COVID-19. Both were randomised, double-blind, placebo-controlled, multicentre studies performed in multiple countries (87 sites in the US, UK, Spain, France and Belgium). In the PROVENT study, 28.4% of participants were recruited from Europe (including UK) and 71.6% from the US. Efficacy was evaluated at two data cut-offs. The first cut-off (June 2021) is the timepoint of the primary efficacy analyses at which 30% of all study participants had become unblinded (PROVENT study, essentially because of the availability of COVID-19 vaccines) or 25 subjects had a primary endpoint event (STORM CHASER study). The second cut-off (August 2021) provides a minimum of 5 months efficacy follow-up data.

1) In the PROVENT study, Evusheld was administered as **pre-exposure prophylaxis** and compared to placebo. Subjects were enrolled in two cohorts. A first cohort of adult subjects considered at increased risk of an inadequate response to active immunisation according to various criteria (e.g. age ≥ 60 years, BMI ≥ 30 kg/m^2, chronic organ disease, immunosuppression). A second cohort included adults < 60 years of age who were considered at higher risk of exposure to infection with SARS-CoV-2 (e.g. healthcare workers, personnel working in high-risk settings conducive to the spread of infection). Participants needed to be unvaccinated and seronegative for SARS-CoV-2 antibodies at the time of inclusion.

The primary endpoint was the first occurrence of symptoms (according to a qualifying list that encompassed typical viral infection signs and symptoms) with a positive SARS-CoV-2 RT-PCR (reverse transcription polymerase chain reaction) test within 183 days after treatment administration. The key secondary endpoint was the incidence of participants with a post-treatment response for SARS-CoV-2 nucleocapsid antibodies (meaning that the key secondary endpoint will detect asymptomatic COVID-19 cases that were not tested by RT-PCR). Other clinically relevant secondary endpoints were targeted at the incidence of severe or critical disease or of COVID-19-related emergency room visits. Overall, the endpoints are clinically meaningful and considered adequate to evaluate the efficacy of the investigated drug. A number of protocol amendments were made during the study, reflecting both the high uncertainty that existed during the pandemic as well as the rollout of vaccines during the study period. None of these raised concerns regarding the validity of the results.

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The primary analysis was performed 30 days after the 25th event had occurred using a Poisson regression model on a “full pre-exposure analysis set” (FAS), i.e. the FAS from which participants with a positive or missing SARS-CoV-2 RT-PCR test were excluded. However, since a PCR test is not required before Evusheld administration, the results from the FAS are considered as more relevant to the real-life indication. Participants could be unblinded during the study to allow the individual to opt for a COVID-19 vaccination. In that case, for the primary analysis, if participants had not experienced a primary endpoint event they were censored at the earlier time of unblinding or vaccination. Since a supportive treatment policy estimand (regardless of vaccination) was provided and consistent with the first estimand, unblinding and vaccination have not affected the results.

A total of 5973 participants were screened, 5254 were randomised (2:1, Evusheld vs Placebo) in the two cohorts. Evaluable patients in the full pre-exposure analysis set (for primary analysis) were 3441 in the Evusheld group and 1731 in the placebo (3460 and 1737 in the same groups for the FAS).

Baseline characteristics were balanced between the groups. Nearly 57% of patients were < 60 years old and approx. 73% were overweight/obese. There was a majority of males (approx. 54%). Overall, approx. 78% of subjects were considered at risk of severe COVID-19 because of their comorbidities, but immunocompromised patients (because of underlying disease or immunosuppressive treatment) were underrepresented (less than 5%).

The primary efficacy analysis at the first June 2021 data cut-off (DCO) (median duration of follow-up of 83 days) indicated that Evusheld significantly reduced the risk of developing symptomatic COVID-19 compared with placebo, with a relative risk reduction of 76.73 (95% CI : 46.05, 89.96 ; $p < 0.001$). It must be noted that the number of events was low: 8/3441 (0.2%) in the Evusheld group vs. 17/1731 (1%) in the placebo. At the second DCO in August 2021 (median duration of follow-up of 196 days in both treatment arms), the relative risk reduction (RRR) was 82.80 (95% CI : 46.79, 91.35), with a number of events of 11/3441 (0.3%) in the Evusheld arm vs. 31/1731 (1.8%) in the placebo arm. A consistent benefit was observed across all pre-specified subgroups (including those at higher risk of severe disease), but the number of events was small. Results for the primary endpoint in the FAS and separately in PCR-positive subjects were provided in response to questions from the EMA. At the August 2021 DCO these indicated that the RRR for the primary endpoint in the FAS analysis was 78.16% and 82.8% in the full pre-exposure analysis set. The FAS results are considered more relevant since a RT-PCR test would not be conducted before Evusheld administration. There were very few cases of PCR-positive subjects at screening. A total of 3/19 and 0/6 PCR-positive participants in the Evusheld and placebo groups, respectively, had primary endpoint events. None of the PCR-positive participants had severe or critical illness.

Key supportive analyses supported the primary endpoint: (i) inclusion of participants who were unblinded and/or vaccinated against COVID-19 (RRR of 77.29 ; 95% CI : 52.01, 89.25 ; $p < 0.001$) and (ii) death from all causes (RRR 68.78, 95% CI : 35.64, 84.86, $p = 0.002$).

The Kaplan-Meier curves for the time to first SARS-CoV-2 RT-PCR-positive symptomatic illness at the primary analysis show that time to event is delayed in the Evusheld group in comparison to placebo:

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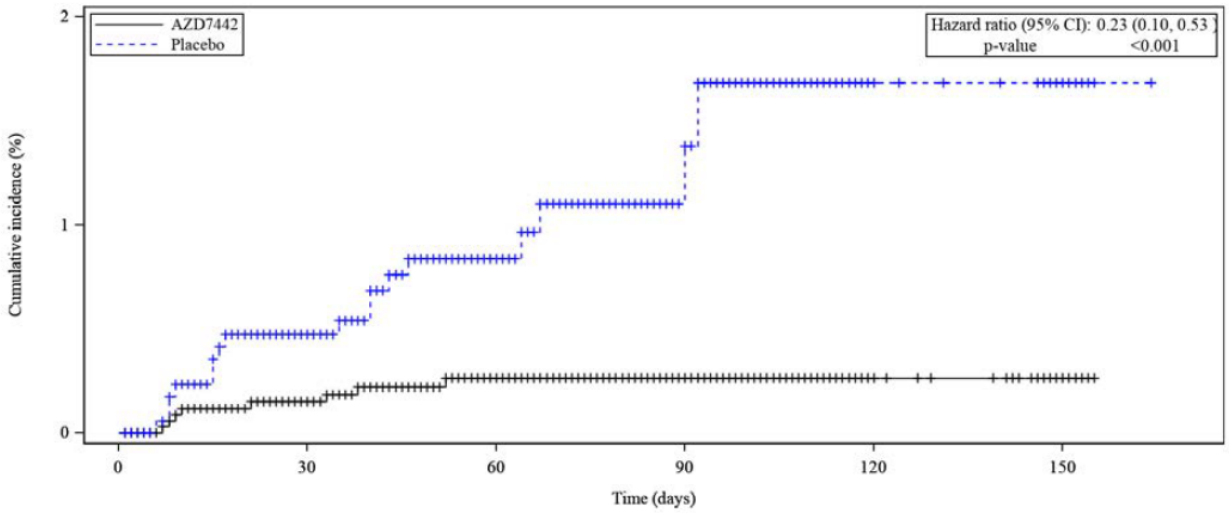
Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post-dose of IMP Kaplan-Meier Curves by Arm, Supplementary Analysis, Full Pre-exposure Analysis Set, Primary Analysis DCO



Number of participants at risk

AZD7442	3441	2964	1759	711	62	18
Placebo	1731	1490	863	340	32	11

Analysis of serological nucleocapsid status, a key secondary endpoint that includes asymptomatic infections that did not lead to a PCR test, showed that Evusheld protected from any SARS-CoV-2 infection, albeit at a lower rate (RRR of 51.07, 95% CI: 10.57, 73.23 ; p = 0.020).

Because of the small number of events, no conclusion can be drawn based on data provided in this submission as to whether Evusheld pre-exposure prophylaxis protects against progression to severe COVID-19, hospitalisation or death in the case of breakthrough infection.

2) The STORM CHASER study assessed the efficacy of Evusheld as **post-exposure prophylaxis** in comparison to placebo. The included participant population consisted of subjects at risk of being infected with SARS-CoV-2 because of a close contact with a confirmed case of SARS-CoV-2 within 8 days. The definition of close contact does not take into account the criteria of distance or duration of exposure, but was essentially based on close living conditions (e.g. same household, dormitory, military barracks, industrial setting), which seems to be a weak point of the study. It must be kept in mind that included patients might have had multiple at-risk exposures during the study period. It has been confirmed by the applicant, in a response to the EMA LoQ, that no information on the type of exposure was collected. This might be unfortunate for epidemiological reasons, but this adequately reflects the real-life context, with known or unknown exposure to symptomatic, asymptomatic, or untested cases. The other inclusion criteria were similar as in the PROVENT study.

Subjects were separated into two cohorts. Cohort 1 consisted of adults ≥ 60 years of age living in long-term care facilities (skilled nursing facilities, assisted living facilities, and independent living facilities for senior adults). In this cohort, potential exposure was defined as the occurrence of SARS-CoV-2 infection, symptomatic or asymptomatic, in another resident of the facility or in a staff member of the facility. Cohort 2 consisted of adults ≥ 18 years of age with potential exposure to an individual with laboratory-confirmed SARS-CoV-2 infection. This could include, but was not limited to, those living in institutional residences, household contacts or healthcare workers. The aim of the initial study

plan was that the percentage of subjects ≥ 60 years of age living in long-term care facilities should make up 50 to 80% of the overall study population. However, because of the rollout of vaccines especially in this vulnerable population, this requirement was removed (with protocol amendments). Hence, the large majority (>99%) of participants included in the study were enrolled under Cohort 2.

The primary endpoint was similar to that in PROVENT, i.e. the first occurrence of symptoms (according to a qualifying list that encompassed typical viral infection signs and symptoms) with a positive SARS-CoV-2 RT-PCR test within 183 days after treatment administration. The key secondary endpoint was to estimate the efficacy of Evusheld for the prevention of severe or critical (i.e. hospitalisation because of pneumonia or hypoxia) symptomatic COVID-19 within Day 183. As for study PROVENT, a secondary endpoint was the incidence of participants with a post-treatment response for SARS-CoV-2 nucleocapsid antibodies (to detect cases with asymptomatic COVID-19 disease and who were therefore not tested by RT-PCR). Of note, patients with a positive or missing SARS-CoV-2 test at screening were not excluded from the primary analysis set (total of 13.8% in the Evusheld and 11.8% in the placebo groups, respectively).

As for PROVENT, in STORM CHASER, participants could be unblinded if they wanted to get a COVID-19 vaccine. They were not censored in the primary analysis. At the primary DCO there were no participants with primary events occurring post unblinding, and only two participants (on placebo arm) discontinued the trial early after unblinding. Thus, the impact of unblinding on primary endpoint analysis is expected to be marginal. However, at the time of the primary analysis, the number of unblinded subjects (in most cases in order to receive COVID-19 vaccination) was higher in the placebo group (14.1%) compared to the Evusheld group (8.2%). Patients knowing that they had received placebo could have been more cautious in their exposure risk than those receiving Evusheld, but this is not expected to change the study results to a meaningful extent.

A total of 1305 subjects were screened and 1110 were randomised (2:1 Evusheld vs Placebo) in the two cohorts. In the full analysis set used for the primary analysis, 749 subjects were in the Evusheld group and 372 in the placebo group.

Baseline characteristics, comorbidities and risk factors were balanced between Evusheld and placebo. Only 20% of patients were ≥ 60 years old. Nearly 50% of patients had comorbidities, and two thirds were considered to be at risk of severe COVID-19 (essentially because of obesity, hypertension and diabetes). Smoking (approx. 19% of participants) was also considered as a risk factor, which is debatable. As previously discussed, the study was initially aimed at including a majority of subjects living in long-term care facilities but, because of the vaccination programme, this number was finally almost negligible (less than 10 subjects). As for PROVENT, the number of immunosuppressed patients was very low (less than 10 subjects).

With the first primary analysis that was performed 30 days after observing 25 events (initially planned after 90 events, but reduced in an amendment because of the availability of vaccines), STORM CHASER did not meet its primary endpoint in the studied population. The relative risk reduction in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness was 33.31 (95% CI: -25.92, 64.68) with Evusheld compared to placebo, and this was not significant with a p = 0.212. The number of events was higher than for PROVENT, with 23/79 (3.1%) participants in the Evusheld arm and 17/372 (4.6%) in the Placebo arm. At the second August 2021 DCO, the readout of the primary endpoint in the full analysis set was borderline significant (RRR 43.21%, 95% CI: 0.14, 67.70, p = 0.049). As for PROVENT, because of the small number of events, no conclusion can be drawn regarding whether Evusheld protects against progression to severe COVID-19 because the number of hospitalisations and death was very low for the exploratory endpoints. The secondary endpoint assessing the presence of antinucleocapsid antibodies (therefore encompassing both symptomatic and asymptomatic infection events) up to Day 183 did not show a difference between the two groups with a similar prevalence of approx. 5%.

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In a predefined subgroup analysis excluding subjects with a positive SARS-CoV-2 RT-PCR at baseline, the primary analysis showed a nominally statistically significant difference for Evusheld compared to placebo, with 6/715 (0.84%) participants with SARS-CoV-2 RT-PCR-positive symptomatic illness in the Evusheld arm compared to 11/358 (3.07%) participants in the placebo arm (RRR 73.17%, 95% CI: 27.10, 90.13). However, the applicant did not propose, in the indication statement, the requirement to perform a RT-PCR test before drug administration to exclude positive participants, and restricted the indication to pre-exposure prophylaxis only.

6.4 Safety

As for efficacy, two DCOs (June 2021 and August 2021) were referenced for the analysis of safety data.

At the first DCO, a total of **4,210** subjects had received 300 mg of Evusheld and **2,108** had received placebo. In the PROVENT and STORM CHASER studies, median age was 57 and 48 years old, respectively, the presence of comorbidities at baseline was 68% vs. 56%, the proportion at risk of developing severe COVID 78% vs 65% and the median follow-up duration was 137 days and 121 days, respectively.

In the pooled study populations, 39.1% (1646/4210) of participants vs. 40.2% (848/2108) experienced an AE and 2.4% (101/4210) vs 2.3% (49/2108) an SAE in the Evusheld and placebo arms, respectively. AEs with a fatal outcome were 0.2% (7/4210, 5/2108) in both groups. A total of 468 participants had AEs assessed as possibly related to the investigational medicinal product (IMP) by the investigator: 327 (7.8%) and 141 (6.7%) in the Evusheld and placebo groups, respectively. The majority of these were mild to moderate in intensity, and headache, fatigue and cough were the most frequent.

In PROVENT there was a numerical imbalance in SAEs involving cardiac disorders and embolic/thrombotic events. In the cardiac disorders System Organ Class (SOC), at the first DCO there were 13 (0.4%) in the Evusheld group vs. 3 (0.2%) in the placebo group. Additional safety information provided by the applicant regarding cardiac disorders up to the August 2021 DCO indicated that, for the PROVENT study, in the Evusheld group there were 9 cases of myocardial infarction (0.26%; 9/3461), one of which was fatal (assessed by the investigator as not related to the IMP). In the placebo group, there were 2 cases of myocardial infarction (0.11% ; 2/1736). Regarding thrombotic events, in the Evusheld group there were 4 cases (0.1%) of pulmonary embolism and 3 cases (0.1%) of deep vein thrombosis, whereas there were none in the placebo group. In STORM CHASER, in the Evusheld group there was 1 case (0.1%, 1/749) of deep vein thrombosis and no cases in the placebo group (0/372). No Cardiac Disorder SAEs were reported in STORM CHASER. All reported SAEs were considered unrelated to the drug by the investigator and occurred in participants with risk factors and comorbidities at baseline. The occurrence of events ranged from 6 days to 197 days, and there was no clear temporal pattern. A causal mechanistic association between Evusheld and these events has not been established. This imbalance is described in the information for healthcare professionals, and an adequate risk management plan is in place.

Hypersensitivity (1.0% in Evusheld and 0.9% in placebo) and injection site reactions (1.3% in Evusheld vs. 1.2% in Placebo) are infrequent and do not raise any concerns. Based on the available (up to Day 58) anti-drug antibody data, there were no treatment-emergent ADA-positive participants in the Evusheld group. There are no safety data for pregnant and breastfeeding women, who were excluded from the study.

Additional safety data from the Phase 2 study D8850C00001, with 50 participants and a median safety follow-up time between 211-271 days, did not yield any safety signals.

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6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

In at-risk patients unable to mount an adequate neutralising antibody response after vaccination (e.g. immunosuppressed persons) or with contraindications to vaccination, the use of monoclonal antibodies as pre-exposure prophylaxis is a useful addition to the available therapeutic arsenal to prevent severe disease outcomes.

The pharmacokinetics of tixagevimab, cilgavimab and Evusheld (combination of both monoclonal antibodies) has been well characterised following i.v. and i.m. administration. Both antibodies have a linear and dose proportional PK over the investigated dose ranges. The PK properties are in line with expectations for monoclonal antibodies with an exogenous target and an extended half-life. Dosing of adolescent patients aged 12 years or older and weighing at least 40 kg was based on exposure matching with adult exposure. As the adult dataset comprised subjects in the respective weight range, this approach is acceptable.

The results of two randomised, double-blind, placebo-controlled pivotal phase III studies with at-risk adult patients with a negative SARS-CoV-2 serology test at screening provided insights regarding the efficacy of Evusheld for the prevention of COVID-19 either as pre- (PROVENT) or post- (STORM CHASER) exposure prophylaxis.

The PROVENT study indicated that, at the primary analysis DCO (median follow-up duration 83 days), Evusheld in comparison to placebo led to a relative risk reduction of RT-PCR-proven symptomatic COVID-19 disease of 76.73%, and of serologically proven disease of 51.07%. In absolute values, this amounted to incidences of 0.2% vs 1.0% and 0.3% vs 1.8% for the same outcomes. The number of deaths related to COVID-19 was 0/3461 and 2/1736 for the Evusheld and placebo arms, respectively. The number of COVID-19-related emergency room visits was very low in both the Evusheld (6/3461, 0.2%) and placebo (3/1736, 0.2%) arms, and no information regarding hospitalisations was captured in the study. The results of the primary analysis are substantiated by the second data cut-off (August 2021 DCO, median follow-up of 183 days). Overall, in the PROVENT study, Evusheld essentially led to a reduction in either PCR-proven or serologically-proven COVID-19 disease but, because of the very low number of events, it cannot be proven that this antibody has a meaningful effect on disease progression (hospitalisations, severe COVID outcomes, death). Since the percentage of importantly immunosuppressed patients was low (<5%), it remains to be seen whether a clinically meaningful impact would be achieved for this population. Importantly, the population included in the PROVENT study consisted of seronegative individuals only, and no firm conclusions on treatment efficacy can be drawn for the seropositive population.

In contrast, the STORM CHASER study did not meet its primary endpoint. Therefore, Evusheld cannot be approved for post-exposure prophylaxis.

In neutralisation assays using authentic SARS-CoV-2 isolates or pseudoviruses, Evusheld retained full to nearly full neutralisation activity against Alpha, Beta, Gamma and Delta VOC, and against Eta, Iota, Kappa, Lambda and Mu variants of Interest (VOI). The pplicant has provided information regarding the efficacy of Evusheld against the Omicron VOC from both the literature and assays performed in various laboratories using either pseudovirus or authentic virus. The reduction in susceptibility against Omicron is up to > 100 fold against BA.1 and BA1.1 but only approx. 5 fold against BA.2. The clinical relevance of reduced neutralising capacity against the Omicron variant remains unknown. The potential duration of protection of at least 6 months was determined by PK, in vitro neutralisation assay data and viral model dynamic modelling. Because lower respiratory tract sampling by bronchoalveolar lavage was not feasible in the presented studies, there are no data regarding the level of antibodies in lung fluid, and assumptions regarding serum:lung fluid ratio were made based on historical literature data. The clinical efficacy of Evusheld against emerging new VOC remains to be determined and will be actively monitored.

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At the June 2021 DCO, in the pooled safety set from the PROVENT and STORM CHASER studies, the overall incidences of AEs and SAEs were similar between Evusheld and placebo. The majority of participants had AEs that were mild to moderate in intensity, and the most frequently reported were headache, fatigue and cough. The proportion of participants with adverse events of special interest (AESI) (anaphylaxis or other serious hypersensitivity reactions, injection site reactions) was of 2.7% for Evusheld and 2.1% for placebo and most of the reported AESI were injection site reactions (Evusheld 2.4%, placebo 2.1%). In STORM CHASER, the incidence of AESI was 0.7% in Evusheld group and 1.3% in placebo group.

In PROVENT, a slight imbalance in both cardiac disorders and embolic/thrombotic events was observed up to the latest DCO (August 2021), with a numerically increased risk of serious cardiovascular events in patients receiving Evusheld compared to those under placebo (0.7% versus 0.3%) and of thrombo-embolic events (0.8% vs 0.6%). Pre-existing conditions, multiple risk factors and concomitant medications render the causality assessment of these AEs difficult.

The overall documentation provided indicates that Evusheld, in the limited at-risk population that either cannot mount an adequate neutralising antibody response or cannot be vaccinated, is effective in preventing symptomatic COVID-19 disease in a pre-exposure setting. There are no prohibitive safety issues. The benefit/risk profile is considered positive.

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7 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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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Evusheld, 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 document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder 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 medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

EVUSHELD is authorised on a temporary basis – see "Properties/Effects" section.

EVUSHELD ®

Composition

Active substances

Tixagevimab, cilgavimab (produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology).

Excipients

Vial containing tixagevimab: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80 (E433), water for injections QS to make 1.5 ml of solution.

Vial containing cilgavimab: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80 (E433), water for injections QS to make 1.5 ml of solution.

Pharmaceutical form and active substance quantity per unit

Solution for injection.

For intramuscular (IM) use.

Each carton of EVUSHELD contains two vials:

- 150 mg of tixagevimab in 1.5 ml (100 mg/ml)
- 150 mg of cilgavimab in 1.5 ml (100 mg/ml)

Indications/Uses

EVUSHELD (tixagevimab and cilgavimab) is indicated for pre-exposure prophylaxis of COVID-19 in adult and adolescents (12 years of age and older weighing at least 40 kg):

- unable to produce an adequate immune response to the SARS-CoV-2 vaccine
  and
- who are not currently infected with SARS-CoV-2 and who have not had recent contact with a person infected with SARS-CoV-2.

See *Dosage/Administration* and *Pharmacokinetics*.

EVUSHELD is not approved for the treatment or post-exposure prophylaxis of COVID-19.

EVUSHELD is not intended as a substitute for vaccination against COVID-19.

EVUSHELD should be used according to official recommendations.

Decisions regarding the use of EVUSHELD for pre-exposure prophylaxis should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viruses, including regional or geographic differences, as well as available information about susceptibility to EVUSHELD (see “Properties/Effects”).

Dosage/Administration

TreatmentAdministration must be initiated and monitored under the supervision of a qualified physician. Administration should take place under conditions where management of an /allergic reaction is possible (see “Warnings and precautions”).

Usual dosage

The recommended dosage is 300 mg of EVUSHELD, administered as two separate and sequential 1.5 ml injections of:

- 150 mg of tixagevimab
- 150 mg of cilgavimab

There are no data on repeated administration available.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Children and adolescents

The safety and efficacy of EVUSHELD in children aged <18 years have not been demonstrated. No data are available.
The recommended dosing regimens are expected to result in comparable serum exposures of tixagevimab and cilgavimab in individuals 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in the clinical trials PROVENT and STORM CHASER (see *Properties/Effects - Pharmacodynamics* and *Pharmacokinetics*).

Mode of administration

EVUSHELD must be administered by a healthcare professional.

EVUSHELD is intended for intramuscular (IM) use only.

Tixagevimab and cilgavimab should be administered as separate sequential IM injections at different injection sites, preferably one injection in each of the gluteal muscles.

Each carton of EVUSHELD contains two vials:

- tixagevimab solution for injection (dark grey vial cap);
- cilgavimab solution for injection (white vial cap).

Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 ml).

Table 1 Dosage of tixagevimab and cilgavimab

EVUSHELD dose (tixagevimab and cilgavimab)	Antibody dose	Number of vials needed	Volume to withdraw from vial
300 mg	Tixagevimab 150 mg	1 vial	1.5 ml
	Cilgavimab 150 mg	1 vial	1.5 ml

Contraindications

Hypersensitivity to the active substances or to any of the excipients listed under *Composition*.

Warnings and precautions

Hypersensitivity, including anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed rarely with other IgG1 monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medicinal products and/or supportive therapy.

Clinically significant bleeding disorders

As with all other intramuscular injections, EVUSHELD should be given with caution to patients with thrombocytopenia or any coagulation disorder.

Cardiovascular and/or thromboembolic events

In the PROVENT study, participants in the EVUSHELD arm experienced more serious cardiovascular

adverse events compared to those in the placebo arm (0.7% versus 0.3%), notably coronary events (e.g. myocardial infarction). A smaller imbalance has been observed for thromboembolic events (0.8% versus 0.6%), notably pulmonary embolism. The majority of the study participants had cardiovascular risk factors and/or history of cardiovascular disease that could explain the occurrence of such events. A causal relationship between EVUSHELD and these events has not been established. The risks and benefits should be considered prior to initiating treatment with EVUSHELD in individuals at high risk for cardiovascular or thromboembolic events. Patients should be advised of signs or symptoms suggestive of a cardiovascular event (notably chest pain, dyspnoea, malaise, feeling lightheaded or faint) and should be instructed to seek immediate medical attention if such symptoms occur.

Antiviral resistance

The clinical trials with EVUSHELD were conducted when the Alpha, Beta, Gamma and Delta variants were predominant. Based on clinical data from PROVENT, the duration of protection following administration of a single EVUSHELD dose (150 mg of tixagevimab and 150 mg of cilgavimab) is estimated to be 6 months
Due to the observed decrease in *in-vitro* neutralization activity against the Omicron subvariants BA.1, BA.1.1 (BA.1+R346K), BA.4 and BA.5, the efficacy of EVUSHELD is uncertain (see Properties/Effects). The effectiveness of EVUSHELD continues to be evaluated. The duration of protection of EVUSHELD for these subvariants is currently not known. The in vitro neutralization activity against the Omicron subvariant BA.2 was in a comparable range as for the Alpha, Beta, Gamma and Delta variants, which were dominant at the time of the PROVENT study.

Interactions

No interaction studies have been conducted.

Pharmacokinetic interactions

Tixagevimab and cilgavimab are not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with other medicinal products that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.
Based on pharmacokinetic (PK) modelling, SARS-CoV-2 vaccination following EVUSHELD administration has no clinically relevant impact on the clearance of EVUSHELD.

COVID-19 vaccines
Tixagevimab and cilgavimab bind to epitopes on the spike protein, which is used as an immunogen in all COVID-19 vaccines. An interaction with COVID-19 vaccinations has not been studied and can therefore not be ruled out. The current vaccination guidelines apply with regard to the timing of vaccination after treatment with monoclonal antibodies against SARS-CoV-2.

Pregnancy, lactation

Pregnancy

There are limited data from the use of tixagevimab and cilgavimab in pregnant women.
Non-clinical reproductive toxicity studies have not been performed with tixagevimab and cilgavimab (see “Preclinical data”).
Human immunoglobulin G1 (IgG1) antibodies are known to cross the placenta. It is not known whether the potential transfer of tixagevimab and cilgavimab represents a benefit or a risk to the developing foetus. EVUSHELD should only be used during pregnancy if the potential benefit justifies the potential risk for the mother and the foetus, taking into consideration all associated health factors. If a woman becomes pregnant during the use of this medicinal product, she must be informed that it is not known whether there is a potential risk for the foetus.

Lactation

It is not known whether tixagevimab and cilgavimab are excreted in human milk. Exposure to the breast-fed child cannot be ruled out.
The developmental and health benefits of breast-feeding should be considered along with the mother’s clinical need for EVUSHELD and any potential adverse effects of EVUSHELD on the breast-fed child.

Fertility

There are no data on the effects of tixagevimab and cilgavimab on human fertility. Effects on male and female fertility were not investigated in the animal studies.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

A total of 4,210 adult participants have received 300 mg EVUSHELD via IM injection in the Phase III prophylaxis studies (PROVENT and STORM CHASER).

List of adverse reactions

Adverse Reactions are organised by MedDRA System Organ Class (SOC) and frequency using the following convention:
"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)
"not known" (frequency cannot be estimated from the available data)
Within each system organ class, the preferred terms are shown in order of decreasing frequency and then decreasing severity in Table 2.

Table 2 Adverse reactions

System organ class	Adverse reaction	Frequency † (
Immune system disorders	Hypersensitivity*	Common (1.0%)
General disorders and administration site conditions	Injection related reaction	Uncommon (0.2%)
Injury, poisoning and procedural complications	Injection site reaction*	Common (1.3%)

† Frequencies are based on exposure to 300 mg EVUSHELD in the pooled data from the prophylaxis studies.
* Grouped terms: Hypersensitivity (including Rash and Urticaria); Injection site reaction (including Injection site pain, Injection site erythema, Injection site pruritus, Injection site reaction and Injection site induration).

Paediatric population

No data are available for paediatric patients <18 years old (see *Dosage/Administration* and *Pharmacokinetics*).
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 ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for overdose with EVUSHELD. An overdose should be treated with general supportive measures, including monitoring of vital signs and observation of the patient's clinical condition.
In clinical trials, doses up to 300 mg IM (150 mg each of tixagevimab and cilgavimab) and 3000 mg intravenously (IV) (1500 mg each of tixagevimab and cilgavimab) have been administered without dose-limiting toxicity.

Properties/Effects

ATC code

J06BD03

Mechanism of action

Tixagevimab and cilgavimab are two recombinant human IgG1κ monoclonal antibodies, with amino acid substitutions to extend antibody half-life and to reduce antibody effector function and potential risk of antibody-dependent enhancement of disease. Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain (RBD) of SARS-CoV-2. Tixagevimab, cilgavimab and their combination bind to spike protein with equilibrium dissociation constants of K_D = 2.76 pM, 13.0 pM and 13.7 pM, respectively, blocking its interaction with the human ACE2 receptor, resulting in a blockade of wildtype virus entry and effectively neutralizing the SARS-CoV-2 virus. Tixagevimab, cilgavimab and their combination blocked RBD binding to the human ACE2 receptor with IC_{50} values of 0.32 nM (48 ng/ml), 0.53 nM (80 ng/ml) and 0.43 nM (65 ng/ml), respectively.

Antiviral activity

In a SARS-CoV-2 virus neutralization assay on Vero E6 cells, tixagevimab, cilgavimab and their combination neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 60.7 pM (9 ng/ml), 211.5 pM (32 ng/ml) and 65.9 pM (10 ng/ml), respectively. These *in vitro* values correlate with *in vivo* clinical effective serum concentrations of 2.2 µg/ml of EVUSHELD.
In cell-based assays, tixagevimab and cilgavimab showed no antibody-dependent cellular cytotoxicity (ADCC), no antibody-dependent cellular phagocytosis (ADCP), no complement-dependent cytotoxicity and no antibody-dependent NK cell activation (ADNKA).

Antibody dependent enhancement (ADE) of infection

In vitro studies showed no antibody-dependent enhancement (ADE).

Antiviral resistance

SARS-CoV-2 or recombinant vesicular stomatitis virus encoding SARS-CoV-2 spike protein were serially passaged in cell cultures in the presence of cilgavimab or tixagevimab individually, or tixagevimab and cilgavimab in combination. Escape variants were identified following passage with cilgavimab, but not with tixagevimab or tixagevimab and cilgavimab in combination. Variants which showed reduced susceptibility to cilgavimab alone included spike protein amino acid substitutions R346I (>200 fold), K444E (>200 fold), K444Q (>200 fold) and K444R (>200 fold). All variants-maintained susceptibility to tixagevimab alone, and tixagevimab and cilgavimab in combination.

Pseudovirus and authentic SARS-CoV-2 neutralization data for SARS-CoV-2 variant substitutions with tixagevimab and cilgavimab in combination are summarized in the table below (Table 3). Data on the neutralization activity of EVUSHELD against pseudovirus and/or live virus SARS-CoV-2 variant strains are summarized in Table 3.

Table 3 Pseudovirus and Authentic SARS-CoV-2 Neutralization Data for SARS-CoV-2 Variant Substitutions with Tixagevimab and Cilgavimab Together

Lineage with Spike Protein Substitutions		Characteristic RBD Substitutions Tested	Reduction in Susceptibility [a]		IC_{50} (ng/ml)	
Pango Lineage (origin)	WHO Label		Pseudovirus[b]	Authentic SARS-CoV-2[c]	Pseudovirus[b]	Authentic SARS-CoV-2[c]
Variants of Concern						
B.1.1.7 (UK)	Alpha	N501Y	No Change[d]	No Change[d]	1.1-9.0	4-39.5
B.1.351 (South Africa)	Beta	K417N:E484K: N501Y	No Change[d]	No Change[d]	5.6-11.4	6.5-256
P.1 (Brazil)	Gamma	K417T:E484K: N501Y	No Change[d]	No Change[d]	1.8-2.7	3.2-8
B.1.617.2 (India)	Delta	L452R:T478K	No Change[d]	No Change[d]	1.9-2.2	3-7.5
AY.1/AY.2 (India)	Delta [+K417N]	K417N:L452R: T478K	No Change[d]	ND	1.9	ND
B.1.1.529 (South Africa)	Omicron BA.1	All identified[e]	132- to 183-fold	12- to 30-fold	51-277	147–278
BA.1.1 (Multiple countries)	Omicron BA.1.1	G339D:R346K: S371L:S373P: S375F:K417N: N440K:G446S: S477N:T478K: E484A:Q493R: G496S:Q489R: N501Y:Y505H	424-fold	176-fold	466	1147
BA.2 (Multiple countries)	Omicron BA.2	G339D:S371F: S373P:S375F: T376A:D405N: R408S:K417N: N440K:S477N: T478K:E484A: Q493R:Q498R: N501Y:Y505H:	No Change[d]	No Change[d]	9.8	35

Lineage with Spike Protein Substitutions		Characteristic RBD Substitutions	Reduction in Susceptibility [a]		IC_{50} (ng/ml)	
BA.2.12.1 (United States)	Omicron BA.2.12.1	G339D:S371F:S373P: S375F:T376A:D405N:R408S:K417N:N440K:L452Q:S477N+T478K:E484A:Q493R:Q498R:N501Y:Y505H	No Change[d]	ND	10.7	ND
BA.3 (Multiple countries)	Omicron BA.3	G339D: S371F:S373P: S375F:D405N:K417N:N440K:G446S:S477N:T478K:E484A:Q493R:Q498R:N501Y:Y505H	16-fold	ND	34.5	ND
BA.4/5 (Multiple countries)	Omicron BA.4/5	G339D:S371F:S373P: S375F:T376A:D405N:R408S:K417N:N440K:L452R:S477N:T478K:E484A:F486V:Q498R:N501Y:Y505H	33- to 65-fold	ND	65-69.4	ND
Variants of Interest						
B.1.525 (Multiple countries)	Eta	E484K	No Change[d]	ND	5-9.5	ND
B.1.526 (United States)	Iota	E484K	No Change[d]	No Change[d]	1.9-5.2	1.0-7.0
B.1.617.1 (India)	Kappa	L452R:E484Q	No Change[d]	No Change[d]	2.5-5.1	2.0-5.0
C.37 (Peru)	Lambda	L452Q:F490S	No Change[d]	ND	1.1	ND
B.1.621 (Colombia)	Mu	R346K:E484K: N501Y	No Change[d]	ND	17.3	ND
Variant Alerts for Further Monitoring						
B.1.427 / B.1.429 (United States)	Epsilon	L452R	No Change[d]	No Change[d]	1.0-4.54	5.0-14.0

Lineage with Spike Protein Substitutions		Characteristic RBD Substitutions	Reduction in Susceptibility [a]		IC_{50} (ng/ml)	
R.1 (Multiple countries)	–	E484K	No Change[d]	ND	4.6	ND
B.1.1.519 (Multiple countries)	–	T478K	No Change[d]	ND	2.3	ND
C.36.3 (Multiple countries)	–	R346S:L452R	No Change[d]	ND	3.9	ND
B.1.214.2 (Multiple countries)	–	Q414K:N450K	No Change[d]	ND	1.6	ND
B.1.619.1 (Multiple countries)	–	N440K:E484K	No Change[d]	ND	7.6	ND
Variants De-Escalated from Further Monitoring						
P.2 (Brazil)	Zeta	E484K	No Change[d]	ND	10.4	ND
B.1.616 (France)	–	V483A	No Change[d]	ND	1.1-1.2	ND
A.23.1 (UK)	–	V367F	No Change[d]	ND	0.5	ND
A.27 (Multiple countries)	–	L452R:N501Y	No Change[d]	ND	1.8	ND
AV.1 (Multiple countries)	–	N439K:E484K	No Change[d]	ND	13.0	ND

[a] Range of reduced *in vitro* potency across multiple sets of co-occurring substitutions and/or testing labs using research-grade assays; mean fold change in half-maximal inhibitory concentration (IC_{50}) of monoclonal antibody required for a 50% reduction in infection compared to wild type reference strain.

[b] Pseudoviruses expressing the entire SARS-CoV-2 spike variant protein and individual characteristic spike substitutions except L452Q were tested, including Alpha (+L455F, E484K, F490S, Q493R, and/or S494P), and Delta (+K417N) harbouring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages.

[c] Authentic SARS-CoV-2 expressing the entire variant spike protein were tested, including Alpha (+E484K or S494P) harbouring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages.

[d] No change: <10-fold reduction in susceptibility.

[e] Omicron spike mutations: A67V, H69-, V70-, T95I, G142D, V143-, Y144-, Y145-, N211-, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F.

ND, not determined; RBD, receptor binding domain.

It is possible that resistance-associated variants to tixagevimab and cilgavimab together could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. Tixagevimab and cilgavimab together retained activity against pseudoviruses harbouring individual SARS-CoV-2 spike substitutions (E484D/K/Q, F490S, Q493R, S494P, K417E/N, D420N, K444Q, V445A, Y453F, L455F, N460K/S/T, F486V, and Q493K) identified in neutralization escape variants of other monoclonal antibodies targeting the RBD of SARS CoV 2 spike protein.

It is not known how pseudovirus or authentic SARS-CoV-2 neutralization susceptibility data correlate with clinical outcome.

Clinical data on antiviral resistance

In the PROVENT study, illness visit sequencing data was available for 21 participants with COVID-19 infection (6 who received tixagevimab and cilgavimab and 15 placebo). At an allele fraction ≥25%, 14 participants were infected with variants of concern or variants of interest, including 8 participants with Alpha (B.1.1.7) (8 placebo), 1 participant with Beta (B.1.351) (1 who received tixagevimab and cilgavimab), 3 participants with Delta (B.1.617.2) (3 placebo), and 2 participants with Epsilon (B.1.429) (2 who received tixagevimab and cilgavimab). Seven additional participants were infected with B.1.375 (1 who received tixagevimab and cilgavimab) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and P681H or Q677P (3 who received tixagevimab and cilgavimab and 3 placebo). Additional spike protein RBD substitutions detected at an allele fraction of 3% included V503F in the tixagevimab and cilgavimab group. Data collection and analysis are not yet complete.

Temporary authorisation

The medicinal product EVUSHELD has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted to an ordinary authorisation.

Pharmacodynamics

In the PROVENT study, following a single 300 mg IM dose of EVUSHELD, neutralizing antibody GMT at 7, 28, 57, and 91 days post-dose were similar to those observed in the Phase I healthy volunteer study and were 16, 22, 17 and 12-fold higher, respectively, than the GMT measured in convalescent plasma from COVID-19 patients (GMT= 30.8).

Clinical efficacy

COVID-19 pre-exposure prophylaxis

PROVENT

PROVENT is an ongoing Phase III, randomized (2:1), double-blind, placebo-controlled clinical trial studying EVUSHELD for the pre-exposure prophylaxis of COVID-19 in adults ≥18 years of age. All participants were individuals considered to be at increased risk for inadequate response to active immunization (due to age ≥60 years, co-morbidity, pre-existing chronic illness, immunocompromised, or intolerant of vaccination) or at increased risk of SARS-CoV-2 infection (due to their location or circumstances at time of enrolment). Participants received either a single dose (administered as two IM injections) of 300 mg EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab, administered

separately) or placebo. The study excluded participants with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening.

The baseline demographics were well balanced across the EVUSHELD and placebo arms. The median age was 57 years (with 43% of participants aged 60 years or older), 46% of participants were female, 73% were White, 3.3% were Asian, 17% were Black/African American, and 15% were Hispanic/Latino. Of the 5,197 participants, 78% had co-morbidities or characteristics associated with an increased risk for severe COVID-19, including immunosuppressive disease (<1%), immunosuppressive medications (3%), diabetes (14%), severe obesity (42%), cardiac disease (8%), chronic obstructive pulmonary disease (5%), chronic kidney disease (5%) and chronic liver disease (5%).

The primary analysis included 5,172 participants who were SARS-CoV-2 RT PCR negative a baseline, of which 3,441 received EVUSHELD and 1,731 received placebo. EVUSHELD significantly (p-value <0.001) reduced the risk of SARS-CoV-2 RT PCR positive symptomatic illness (COVID-19) when compared to placebo (Table 4). The median follow-up time post-administration was 83 days.

Table 4 Incidence of COVID-19 (Full Pre-Exposure Analysis Set)

	N	**Number of events[a], n (%)**	**Relative Risk Reduction, % (95% CI)**
EVUSHELD 300 mg[b]	3,441	8 (0.2%)	77% (46 - 90)
Placebo	1,731	17 (1.0%)	

CI = Confidence Interval, N = number of participants in analysis.

[a] Primary endpoint, a participant was defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurred after administration and prior to Day 183.

[b] 300 mg IM (150 mg tixagevimab and 150 mg cilgavimab).

Efficacy was consistent across the pre-defined sub-groups, including age, sex, ethnicity and baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19.

There was a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause for participants who had received EVUSHELD (12/3,441) compared with placebo (19/1,731), relative risk reduction 69% (95% CI: 36, 85); p value= 0.002.

Efficacy was assessed in participants who had no serological evidence of previous SARS-CoV-2 infection (SARS-CoV-2 nucleocapsid antibody negative) at baseline. EVUSHELD significantly reduced the risk of SARS-CoV-2 infection (symptomatic or asymptomatic, SARS-CoV-2 nucleocapsid antibody positive at any time post baseline) when compared to placebo; SARS-CoV-2 nucleocapsid antibodies were observed in 0.7% (21/3,123) of participants who received EVUSHELD and 1.3%

(21/1,564) of participants who received placebo (relative risk reduction 51%, 95% CI: 11, 73; p-value = 0.020).

Among participants who received EVUSHELD, there were no severe/critical COVID-19 events (defined as SARS-CoV-2 RT-PCR positive symptomatic illness characterised by a minimum of either pneumonia [fever, cough, tachypnoea or dyspnoea, and lung infiltrates] or hypoxemia [SpO2 <90% on ambient air and/or severe respiratory distress] and a WHO Clinical Progression Scale score of 5 or higher) compared to one event (0.1%) among participants who received placebo.
An additional data cut-off was conducted to provide post-hoc updated safety and efficacy analyses; the median follow-up was 6.5 months for participants in both the EVUSHELD and placebo arms. The relative risk reduction of SARS-CoV-2 RT-PCR positive symptomatic illness was 83% (95% CI 66-91), with 11/3,441 [0.3%] events in the EVUSHELD arm and 31/1,731 [1.8%] events in the placebo arm,. These results are consistent with the duration of protection predicted by population pharmacokinetic (PK) modelling (see *Pharmacokinetics*). Among participants who received EVUSHELD, there were no severe/critical COVID-19 events, compared to five events among participants who received placebo. The Kaplan-Meier curves for time to first SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of EVUSHELD or placebo showed continuous separation of the curves, beginning at Day 5 and persisting over the entire 180-day observation period. The hazard ratio is shown to favour the EVUSHELD arm at 0.17 (95% CI: 0.08, 0.33) with a p-value of less than 0.001.

Pharmacokinetics

The pharmacokinetics of tixagevimab and cilgavimab are comparable, linear and dose-proportional between 150 mg and 1500 mg tixagevimab or cilgavimab following a single IV administration.

Absorption

After a single 300 mg IM dose (150 mg of each antibody) in healthy volunteers, the estimated absolute bioavailability was 68.5% for tixagevimab and 65.8% for cilgavimab.

Based on pharmacokinetic/pharmacodynamic models, it is estimated that 90% of patients achieve a protective serum concentration within 24 hours.

Distribution

Based on PK modelling, the central volume of distribution was 2.72 L for tixagevimab and 2.48 L for cilgavimab. The peripheral volume of distribution was 2.64 L for tixagevimab and 2.57 L for cilgavimab.

Metabolism

Tixagevimab and cilgavimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

Elimination

Clearance (CL) was 0.041 L/day for tixagevimab and 0.041 L/day for cilgavimab, with inter-subject variability of 21% and 29% respectively. The estimated population median terminal elimination half-life was 89 days for tixagevimab and 84 days for cilgavimab.

In PROVENT, following a single 300 mg IM dose of EVUSHELD, the geometric mean serum concentration was 23.4 µg/ml (geoSD: 1.9) on Day 29 and 12.2 µg/ml (geoSD: 1.4) on Day 183.

Kinetics in specific patient groups

Renal impairment

No specific studies have been conducted to examine the effects of renal impairment on the pharmacokinetics of tixagevimab and cilgavimab.
Tixagevimab and cilgavimab are not eliminated intact in the urine, thus renal impairment is not expected to significantly affect the exposure of tixagevimab and cilgavimab. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.
Based on population PK analysis, there is no difference in the clearance of tixagevimab and cilgavimab in patients with mild (N=978) or moderate (N=174) renal impairment compared to patients with normal renal function. In the population PK model, there were insufficient participants with severe renal impairment (N=21) to draw conclusions.

Hepatic impairment

No specific studies have been conducted to examine the effects of hepatic impairment on the PK of tixagevimab and cilgavimab. The impact of hepatic impairment on the PK of tixagevimab and cilgavimab is expected to be low.
Tixagevimab and cilgavimab are expected to be catabolised by multiple tissues through proteolytic degradation into amino acids and recycling into other proteins, therefore hepatic impairment is not expected to affect the exposure of tixagevimab and cilgavimab.

Elderly patients

Of the 2,560 participants in the pooled PK analysis, 21% (N=534) were 65 years of age or older and 4.2% (N=107) were 75 years of age or older. There is no clinically meaningful difference in the PK of tixagevimab and cilgavimab in geriatric subjects (≥65 years) compared to younger individuals.

Children and adolescents

The PK of tixagevimab and cilgavimab in individuals <18 years old have not been evaluated.
Using population PK modelling and simulations, the recommended dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab in paediatric individuals aged 12 years or older who weigh at least 40 kg as observed in adult individuals, since adults with similar body weight have been included in the PROVENT clinical trial.

Patients with high body weight
Based on population PK analysis, a decrease in EVUSHELD serum concentrations with increasing body weight was observed. After a dose of 150 mg tixagevimab and 150 mg cilgavimab, the expected mean serum concentration in an adult weighing >95 kg is 37% lower than in an adult weighing 65 kg.

Other special populations

Based on a population PK analysis, sex, age, race, ethnicity, cardiovascular disease, diabetes and immunocompromise had no clinically relevant effect on the PK of tixagevimab and cilgavimab.

Preclinical data

Non-clinical data reveal no special hazard for humans based on studies of tissue binding and a single-dose toxicity study in cynomolgus monkeys including assessment of safety pharmacology and local tolerance.

In tissue cross reactivity studies using human adult and foetal tissues, no binding was detected.

Carcinogenicity, mutagenicity, and reproductive toxicology studies have not been conducted.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

Shelf life

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

Shelf life after opening

The solutions for injection do not contain a preservative and, therefore, the prepared syringes should be administered immediately. If immediate administration is not possible and the prepared tixagevimab and cilgavimab syringes need to be stored, the total time from vial puncture to administration should not exceed 4 hours, either:

- in a refrigerator at 2ºC to 8ºC
- or at room temperature up to 25ºC

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze. Do not shake.
Keep the vial in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

Visually inspect the vials for particulate matter and discolouration. Both tixagevimab and cilgavimab are clear to opalescent, colourless to slightly yellow solutions of pH 6.0. Discard the vials if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vials.
The solutions for injection do not contain a preservative. Any unused solution should be discarded.

Authorisation number

68704 (Swissmedic)

Packs

Each carton contains two vials:
Tixagevimab
1.5 ml of solution for injection in a single-dose clear glass vial, closed with a chlorobutyl elastomeric stopper and sealed with a dark-grey aluminium flip-off top. [A]
Cilgavimab
1.5 ml of solution for injection in a single-dose clear glass vial, closed with a chlorobutyl elastomeric stopper sealed with a white aluminium flip-off top. [A]

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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August 2022