Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-269 AZD3152

Stand: November 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
AZD3152 [Präexpositionsprophylaxe von COVID-19] **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Nutzenbewertung nach §35a SGB V • Tixagevimab/Cilgavimab; Beschluss vom 2. November 2023
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
AZD3152	wird angewendet zur Präexpositionsprophylaxe einer Coronavirus-19-Erkrankung (coronavirus disease 2019, COVID-19) bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht
Tixagevimab/Cilgavimab J06BD03 Evusheld®	EVUSHELD® wird angewendet zur Präexpositionsprophylaxe einer Coronavirus-19- Erkrankung (Coronavirus Disease 2019, COVID-19) bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht.
Casirivimab/Imdevimab J06BD07 Ronapreve® nicht in Verkehr	Ronapreve® wird angewendet zur Prophylaxe von COVID-19 bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-269 (AZD3152)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	7. November 2023

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Abkürzungsverzeichnis

AE	adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	Emergency Care Research Institute
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
mAbs	monoclonal antibodies
NICE	National Institute for Health and Care Excellence
PrEP	pre-exposure prophylaxis
OR	Odds Ratio
RR	Relatives Risiko
SAE	serious adverse event
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Präexpositionsprophylaxe einer Coronavirus-19-Erkrankung (coronavirus disease 2019, COVID-19) bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Prä- oder Post-Expositions-Prophylaxe einer COVID-19-Erkrankung* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 25.06.2021 durchgeführt, die folgenden am 20.07.2022 und 17.10.2023. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 3173 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 7 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Hirsch C et al., 2022 [2].

SARS-CoV-2-neutralising monoclonal antibodies to prevent COVID-19

Fragestellung

To assess the effects of SARS-CoV-2-neutralising mAbs, including mAb fragments, to prevent infection with SARS-CoV-2 causing COVID-19; and to maintain the currency of the evidence, using a living systematic review approach.

Methodik

Population:

- people of any age, gender, or ethnicity
- participants without defined exposure, or with potential exposure to SARS-CoV-2, but who did not have a confirmed diagnosis of COVID-19 (virus antigens or RNA detected). For PrEP, we included participants regardless of SARSCoV-2 antibody serostatus and for PEP, we included SARS-CoV-2 antibody seronegative participants.
- We did not exclude studies based on age, gender, ethnicity, or setting. We excluded studies that evaluated mAbs to prevent infection from other coronavirus diseases (e.g. SARS or MERS), or other viral diseases, such as influenza. If studies enrolled populations with mixed viral diseases, we only included these if trial authors provided subgroup data for participants with COVID-19.

Intervention:

We included the following interventions.

• SARS-CoV-2-neutralising mAbs, including mAb fragments.

• Combinations of SARS-CoV-2-neutralising mAbs.

Kontrolle:

• Any mAb prophylaxis compared with a control intervention, for example, vaccinations, drug prophylaxis (including but not limited to hydroxychloroquine, remdesivir), standard or hyperimmune immunoglobulin, convalescent plasma, other prevention strategies (e.g. protective clothing, face masks, social distancing), complementary medicine (e.g. quercetin, elderberry, zinc), or others.

• Any mAb prophylaxis compared with no prophylaxis or placebo.

Co-interventions were allowed, but these must have been comparable between intervention groups.

We included studies that compared several mAbs or mAb fragments with each other and another prophylaxis, placebo or no prophylaxis, as well as studies that compared several doses of one type of mAb or mAb fragments with another prophylaxis, placebo, or no prophylaxis.

Endpunkte:

confirmed COVID-19 infections;

development of COVID-19 symptoms;

death from any cause; – hospital admission; – quality of life; – unwanted effects, such as infections and cardiac disorders; – serious unwanted effects, such as life-threatening, hospitalisation, disability, or death.

Recherche/Suchzeitraum:

- Cochrane COVID-19 Study Register, MEDLINE, Embase, and three other databases on 27 April 2022

Qualitätsbewertung der Studien:

- RoB 2 tool; GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- Pre-exposure prophylaxis (2 Studien): Isa 2021; PROVENT

Charakteristika der Population:

- PROVENT: One study evaluated tixagevimab/cilgavimab versus placebo in participants exposed to SARS-CoV-2 wild-type, Alpha, Beta, and Delta variant. About 39.3% of participants were censored for efficacy due to unblinding and 13.8% due to vaccination.
- ISA 2021: One study evaluated casirivimab/imdevimab versus placebo in participants who may have been exposed to SARS-CoV-2 wild-type, Alpha, and Delta variant. About 36.5% of participants opted for SARS-CoV-2 vaccination and had a mean of 66.1 days between last dose of intervention and vaccination.

Qualität der Studien:

- Siehe Summary of findings (Anhang)

Studienergebnisse:

- Pre-exposure prophylaxis Tixagevimab/cilgavimab versus placebo

  Within six months, tixagevimab/cilgavimab probably decreases infection with SARS-CoV-2 (risk ratio (RR) 0.45, 95% confidence interval (CI) 0.29 to 0.70; 4685 participants; moderate-certainty evidence), decreases development of clinical COVID-19 symptoms (RR 0.18, 95% CI 0.09 to 0.35; 5172 participants; high-certainty evidence), and may decrease admission to hospital (RR 0.03, 95% CI 0 to 0.59; 5197 participants; low-certainty evidence). Tixagevimab/cilgavimab may result in little to no difference on mortality within six months, all-grade AEs, and SAEs (lowcertainty evidence). Quality of life was not reported.

- Casirivimab/imdevimab versus placebo

  Within six months, casirivimab/imdevimab may decrease infection with SARS-CoV-2 (RR 0.01, 95% CI 0 to 0.14; 825 seronegative participants; low-certainty evidence) and may decrease development of clinical COVID-19 symptoms (RR 0.02, 95% CI 0 to 0.27; 969 participants; low-certainty evidence). We are uncertain whether casirivimab/imdevimab affects mortality regardless of the SARS-CoV-2 antibody serostatus. Casirivimab/imdevimab may increase all-grade AEs slightly (RR 1.14, 95% CI 0.98 to 1.31; 969 participants; low-certainty evidence). The evidence is very uncertain

about the effects on grade 3 to 4 AEs and SAEs within six months. Admission to hospital and quality of life were not reported.

Anmerkung/Fazit der Autoren

For PrEP, there is a decrease in development of clinical COVID-19 symptoms (high certainty), infection with SARS-CoV-2 (moderate certainty), and admission to hospital (low certainty) with tixagevimab/cilgavimab. There is low certainty of a decrease in infection with SARS-CoV-2, and development of clinical COVID-19 symptoms; and a higher rate for all-grade AEs with casirivimab/imdevimab.

Although there is high-to-moderate certainty evidence for some outcomes, it is insufficient to draw meaningful conclusions. These findings only apply to people unvaccinated against COVID-19. They are only applicable to the variants prevailing during the study and not other variants (e.g. Omicron). In vitro, tixagevimab/cilgavimab is effective against Omicron, but there are no clinical data. Bamlanivimab and casirivimab/imdevimab are ineffective against Omicron in vitro.

Further studies are needed and publication of four ongoing studies may resolve the uncertainties.

Kommentare zum Review

- Es werden hier nur die Ergebniss zur PreP dargestellt.
- Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:
  - Suribhatla R et al., 2022 [6]
  - Bartoszko JJ et al., 2021 [1]

3.2 Systematische Reviews

Soeroto AY et al., 2023 [5].

Efficacy and safety of tixagevimab-cilgavimab as preexposure prophylaxis for COVID-19: A systematic review and meta-analysis

Fragestellung

to analyze the effectiveness and safety of tixagevimab-cilgavimab (Evusheld) as pre-exposure prophylaxis against COVID-19

Methodik

Population:

- individuals without SARS-CoV-2 infection (proved by negative RT-PCR or antigen test results) at the start of the study or at the time of enrollment with the inadequate immune response risk from SARS-CoV-2 vaccine (e.g. immunocompromised individuals, organ transplant recipients, patients with malignancy);

Intervention:

- receiving the combination of tixagevimab and cilgavimab at any dosage and through any route of administration during the study period as a preventive measure for COVID-19;

Komparator:

- other agents, standard of care (SOC) or placebo

Endpunkte:

- SARS-CoV-2 infection rates with/without secondary outcomes (hospitalization rate, COVID-19 severity, and COVID-19 mortality)

Recherche/Suchzeitraum:

- PubMed, Scopus, Europe PMC, and ClinicalTrials.gov until 3 September 2022

Qualitätsbewertung der Studien:

- RoB v2 instrument
- NOS rating scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 Kohortenstudien zur Präexpositionsprophylaxe der Omicron-Variante

Charakteristika der Population/Studien:

- Siehe Anhang

Qualität der Studien:

TABLE 3 Newcastle-Ottawa quality assessment of observational studies

First author, year	Study design	Selection[a]	Comparability[b]	Outcome[c]	Total score	Remark
Al Jurdi A et al.[25] 2022	Cohort	3	2	2	7	Good
Bertrand D et al.[26] 2022	Cohort	3	2	2	7	Good
Kaminski H et al.[27] 2022	Cohort	3	2	2	7	Good
Kertes J et al.[28] 2022	Cohort	3	2	3	8	Good
Young-Xu et al.[29] 2022	Cohort	3	2	3	8	Good

[a](1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at start of study.

[b](1) comparability of cohorts on the basis of design or analysis, (maximum two stars).

[c](1) assessment of outcome; (2) was follow-up long enough for outcomes to occur; (3) adequacy of follow up of cohorts.

Studienergebnisse zur Omicron-Variante:

- five cohort studies were conducted during predominantly Omicron variant of SARS-CoV-2:
- Our meta-analysis still revealed that a combination tixagevimab and cilgavimab may reduce the rate of SARS-CoV-2 infection during predominantly Omicron variant when compared with those who only receive SOC or placebo (OR: 0.26; 95% CI: 0.15–0.47, $p < 0.00001$, $I_2 = 78\%$, random effect models)

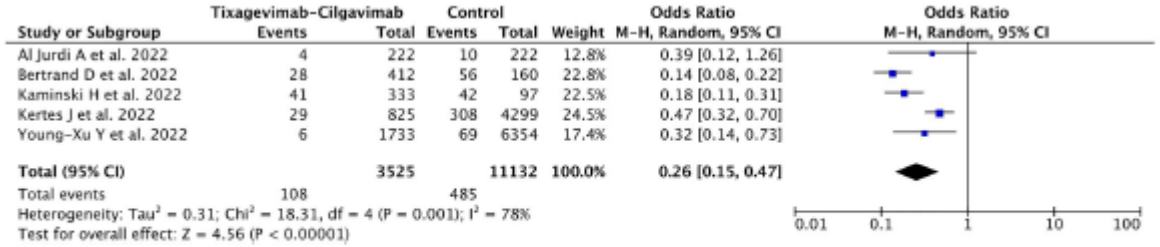

FIGURE 3 Forest plot that demonstrates the sensitivity analysis result after removing the study by Levin MJ et al. for the rate of SARS-CoV-2 infection.

Anmerkung/Fazit der Autoren

Our study showed that combination of tixagevimab and cilgavimab may effectively reduce the rate of SARS-CoV-2 infection better than a placebo or SOC. In those who were still getting infected with COVID-19 after the intervention, the rate of hospitalization, severe COVID-19, and mortality from COVID-19 were significantly lowered in the tixagevimab-cilgavimab group than in the control group. Tixagevimab-cilgavimab was also relatively safe as there were no treatment-associated serious adverse events reported. Our study suggested that combination of tixagevimab-cilgavimab may be offered as pre-exposure prophylaxis agents, especially in those who can't be vaccinated or those who have inadequate immune response to the SARS-CoV-2 vaccine.

Kommentare zum Review

- Es wurden nur die Ergebnisse zur Omicron-Variante dargestellt. In die Meta-Analyse wurden Kohortenstudien eingeschlossen, da es keine RCT zu dieser Fragestellung vorlagen.

3.3 Leitlinien

Infectious Diseases Society of America (IDSA), 2023 [3].

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

Zielsetzung/Fragestellung

to regularly review the evidence and make recommendations about the treatment and management of persons with COVID-19.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: unklar, ob ein Patientenvertreter teilgenommen hat;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu.

Recherche/Suchzeitraum:

- May 31, 2022

LoE/GoR

- Risk of bias was assessed using the Cochrane Risk of Bias Tool for RCTs
- Grading of Recommendations Assessment, Development and Evaluation (GRADE)
- As per GRADE methodology, recommendations are labeled as “strong” or “weak/conditional”. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations.

Empfehlungen

Hydroxychloroquine for Prophylaxis

- **Recommendation 3:** In persons exposed to COVID-19, the IDSA guideline panel recommends against hydroxychloroquine. (Strong recommendation, Moderate certainty of evidence)

Neutralizing Antibodies for Pre-Exposure Prophylaxis

- As of 1/26/2023, based on CDC Nowcast data, fewer than 10% of circulating variants in the US are susceptible to tixagevimab/cilgavimab (Evusheld), the sole product that has been available for pre-exposure prophylaxis. Tixagevimab/cilgavimab is therefore no longer authorized for use in the US until further notice by FDA.

World Health Organization (WHO), 2023 [7].

WHO Living guideline: Drugs to prevent COVID-19; 24 March 2023

Zielsetzung/Fragestellung

What is the role of drugs for preventing COVID-19?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- living systematic review, letzte Aktualisierung: 24 March 2023

LoE/GoR

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Sonstige methodische Hinweise

- This is a living guideline, so the recommendation included here will be updated, and new recommendations will be added on other prophylactic interventions for COVID-19.

Recommendation

6. Recommendations for prophylaxis

6.1 Hydroxychloroquine

Strong recommendation against

Updated

We recommend against administering hydroxychloroquine prophylaxis to individuals who do not have COVID-19 (strong recommendation)

Remark: This recommendation applies to individuals with any baseline risk of developing COVID-19 and any hydroxychloroquine dosing regimen.

Practical Info

Given the strong recommendation against using hydroxychloroquine prophylaxis for individuals who do not have COVID-19, practical considerations were felt to be less relevant here.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Used prophylactically, hydroxychloroquine has no or little effect on death and hospital admission (high certainty), and has no or little effect on laboratory-confirmed SARS-CoV-2 infection (high certainty). It increases the risk of adverse effects leading to discontinuation of the drug (high certainty).

There was no subgroup effect according to known exposure to a person with SARS-CoV-2 infection or hydroxychloroquine dose regimen (extremely low event rates precluded investigation of subgroup effects for mortality). The panel therefore assumed similar relative effects across subgroups.

Certainty of the Evidence

High

Certainty was high for all key outcomes.

Values and preferences — We expect few to want the intervention

Given the high certainty of the evidence, the panel inferred that almost all informed individuals would choose not to have the intervention and would decline hydroxychloroquine.

Resources and other considerations — Important negative issues

Hydroxychloroquine is relatively inexpensive and is widely available, including in low-resource settings. Although the cost may be low per patient, the overall cost of delivering a prophylactic intervention on a large scale may be significant. Moreover, the panel raised concerns about diverting hydroxychloroquine stocks away from patients with other conditions for whom this medication is indicated *(36)*.

Justification

When moving from the evidence to the strong recommendation against the use of hydroxychloroquine to prevent COVID-19-related outcomes, the panel emphasized the evidence suggesting no or little effect on mortality and hospital admission along with an increased risk of adverse effects. For a more detailed discussion about how high certainty of no or little effect may be achieved with low event rates and the steps separating administration of a prophylactic intervention from the occurrence of an important clinical endpoint, please refer to the discussion on special methodological considerations relevant to this guideline (section 4.1). Of note, when updating this recommendation, the panel considered data on mortality from 12 trials (n=8379) randomizing participants to hydroxychloroquine or standard care/placebo. This strengthened the panel's certainty that prophylactic interventions, in be oriented to evaluate other more promising prophylactic interventions. Notwithstanding, the panel also reiterated that a strong recommendation signifies that its members believed that individuals would choose not to receive hydroxychloroquine prophylaxis, which implies that there may be exceptions. The panel did not find any evidence of a subgroup effect as a function of known exposure to SARS-CoV-2 infection or by dose Hydroxychloroquine crosses the placental barrier and there are concerns that it may lead to retinal damage in neonates. the populations studied in these clinical trials, will not lead to large reductions in mortality given their risk of death is very small. Although certain subgroups of vulnerable individuals may have been under-represented in previous hydroxychloroquine prophylaxis trials, the panel maintained its view that, given the existing evidence, it would be extremely unlikely that hydroxychloroquine would lead to a meaningful mortality reduction even in those subgroups, and highly unlikely that future trials would successfully enrol individuals that previous trials have not been able to enrol thus far. In light of this evidence, the panel did not anticipate important variability when it comes to patient values and preferences. In addition, the panel decided that contextual factors such as resources, feasibility, acceptability and equity for countries and health care systems were unlikely to alter the recommendation. The panel acknowledged that a strong recommendation against hydroxychloroquine to prevent COVID-19 indicates that this area is no longer a research priority and that resources devoted to clinical research should rather almost all well-informed

Subgroup analyses of hydroxychloroquine. Of note, for trials that enrolled participants without a known exposure, the weekly dose of hydroxychloroquine was used as the variable of interest to account for longer term prophylaxis; for trials that enrolled participants following a known exposure to SARS-CoV-2, the cumulative dose was used as the variable of interest to reflect shorter term prophylaxis. As no subgroup effect modification was found, the strong recommendation is applicable across risk groups and dose regimens of hydroxychloroquine. The trials included participants from North and

South America and Europe who either had a known exposure to a person with SARS-CoV-2 infection or who were considered at risk given their professional occupations (e.g. health care workers).

Applicability Regarding special populations, none of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children would respond any differently to prophylactic hydroxychloroquine. There were similar considerations in regards to pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently to other adults.

Clinical Question/ PICO

Population: Individuals at risk of COVID-19
Intervention: Hydroxychloroquine
Comparator: Standard care

Summary

The Table shows the characteristics of the RCTs evaluating hydroxychloroquine compared with standard care/placebo included in the LNMA informing the recommendation *(3)*. The GDG was informed by 12 trials (n=8379 participants) when they made this recommendation in December 2022 *(9)(10)(11)(12)(13)(14)(15)(16)(17)(18)(19)(20)*. The most recent LNMA publication *(3)* contains an additional trial comparing hydroxychloroquine to active interventions *(35)*.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Hydroxychloroquine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality	Based on data from 6,822 participants in 7 studies. (Randomized controlled)	3 per 1000 Difference:	3 per 1000 **0 fewer per 1000** (CI 95% 3 fewer – 2 more)	High	Hydroxychloroquine has little or no effect on mortality.
Admission to hospital	Based on data from 7,432 participants in 10 studies. (Randomized controlled)	3 per 1000 Difference:	1 per 1000 **2 fewer per 1000** (CI 95% 6 fewer – 2 more)	High	Hydroxychloroquine has little or no effect on hospital admission.
Laboratory-confirmed SARS-CoV-2 infection	Odds ratio 0.95 (CI 95% 0.62 – 1.32) Based on data from 8,379 participants in 12 studies.	62 per 1000 Difference:	59 per 1000 **3 fewer per 1000** (CI 95% 24 fewer – 19 more)	High	Hydroxychloroquine has little or no effect on laboratory-confirmed COVID-19 infection.
Adverse events leading to discontinuation	Based on data from 6,153 participants in 9 studies.	22 per 1000 Difference:	28 per 1000 **6 more per 1000** (CI 95% 2 more – 10 more)	High	Hydroxychloroquine has a small increase in adverse effects leading to discontinuation.

6.2 Tixagevimab-cilgavimab

Conditional recommendation against

New

We suggest not to use tixagevimab-cilgavimab in individuals who do not have COVID-19 (conditional recommendation).

Remark: This recommendation applies to all individuals who do not have COVID-19.

Practical Info

Given the conditional recommendation against using tixagevimab-cilgavimab prophylaxis for individuals who do not have COVID-19, practical considerations were felt to be less relevant here.

Evidence To Decision

Benefits and harms

The panel reviewed clinical trial evidence, available via the LNMA (3), in parallel with subsequent in vitro data on virus neutralization efficacy of tixagevimab-cilgavimab (see section 6.2.1). The panel noted that while the clinical trial results suggested prophylactic use of tixagevimab-cilgavimab reduced the occurrence of laboratory-confirmed symptomatic COVID-19 (i.e. individuals were only tested if they developed symptoms). Tixagevimab-cilgavimab were not associated with reductions in hospital admissions or deaths. Moreover, the panel also concluded that these modest benefits represent the best-case scenario obtained under bygone conditions since new SARS-CoV-2 sublineages have since replaced the former Omicron sublineages that could be neutralized by tixagevimab-cilgavimab.

Certainty of the Evidence

Having concluded that recently emerged in vitro evidence rendered the clinical trial results obsolete, the panel abstained from rating the certainty of the underlying evidence.

Values and preferences

The GDG inferred that, in the absence of compelling evidence of clinical effectiveness for the currently circulating SARS-CoV-2 sublineages, the majority of informed individuals would choose not to receive tixagevimab-cilgavimab.

Resources and other considerations

The panel placed a low value on minor health benefits associated with a costly intervention of limited availability and requiring parenteral administration. Conversely, the panel placed a high value on preserving resources for interventions with a high certainty of benefit and noted the availability of effective therapeutic options.

The conditional recommendation against the use of tixagevimab-cilgavimab is supported by the requirement for expertise to offer such prophylaxis, and the availability of oral antiviral therapies recommended for treatment.

Justification

When moving from the evidence to the conditional recommendation against the use of tixagevimab-cilgavimab to prevent COVID-19-related outcomes, the panel emphasized in vitro evidence reducing the applicability of tixagevimab-cilgavimab prophylaxis trial data to the point of precluding any certainty rating. In this context, all panel members agreed on

the direction of the recommendation, but not on the strength of the recommendation. Approximately half of the panel voted for a strong recommendation also because they believed that it would be extremely unlikely for previous SARS-CoV-2 sublineages to re-emerge. Moreover, in the event that new sublineages might be neutralized by tixagevimab-cilgavimab as former sublineages were, in vitro neutralization, a sine qua non condition for clinical effectiveness, would not guarantee clinical effectiveness. Panel members who voted for a conditional recommendation underscored that it nonetheless remained theoretically possible that former sublineages would continue to cause COVID-19 in certain regions and that, assuming that real-time monitoring of the prevalence of SARS-CoV-2 sublineages was available, a significant number of extremely vulnerable individuals may chose to receive prophylactic tixagevimab-cilgavimab. All panel members agreed that any prophylactic use of this intervention should be restricted to extremely vulnerable individuals, i.e. those who highly unlikely to mount an immune response following COVID-19 vaccination and who, due to a limited physiological reserve, are at increased risk of developing severe manifestations of COVID-19.

Noting that similar in vitro evidence led to a strong recommendatIon against the therapeutic use of human monoclonal antibodies, the panel noted that while there exists no alternative for prophylaxis, while patients who develop COVID-19 have other therapeutic options.

Clinical Question/ PICO

Population:	Individuals at risk of COVID-19
Intervention:	Tixagevimab + cilgavimab
Comparator:	Standard care/placebo

Summary

The Table shows the characteristics of the RCT evaluating tixagevimab-cilgavimab compared with standard care/placebo included in the LNMA informing the recommendation [3].

Outcome Timeframe	Study results and measurements	Comparator Standard care/ placebo	Intervention Tixagevimab + cilgavimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality	Based on data from 5,197 participants in 1 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000** (CI 95% 30 fewer – 28 more)		
Laboratory-confirmed SARS-CoV-2 infection	Odds ratio 0.23 (CI 95% 0.07 – 0.74) Based on data from 5,172 participants in 1 studies. (Randomized controlled)	65 per 1000 Difference:	17 per 1000 **48 fewer per 1000** (CI 95% 62 fewer – 17 fewer)		
Admission to hospital	Based on data from 5,197 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	0 per 1000 **4 fewer per 1000** (CI 95% 35 fewer – 27 more)		
Serious adverse events	Based on data from 5,197 participants in 1 studies. (Randomized controlled)	37 per 1000 Difference:	37 per 1000 **0 fewer per 1000** (CI 95% 11 fewer – 10 more)		

6.2.1 Mechanism of action

Tixagevimab (COV2-2196, AZD8895) and cilgavimab (COV2-2130, AZD1061) are a combination (Evusheld, AZD7442) of human monoclonal antibodies that bind to nonoverlapping regions of the receptor-binding domain (RBD) of the SARS-CoV-2 Spike protein *(37)*. Both antibodies are Fc-engineered IgGs, whereby amino acid substitutions increase pharmacokinetic half-life by 2 to 4-fold, but also reduce recruitment of effector functions *(38)*. The combination of tixagevimab and cilgavimab administered prophylactically as intravenous infusion prevented infection animal models by ancestral SARS-CoV-2 *(39)* but animal data for currently circulating variants are unavailable. Resistance to both antibodies occurred when historical variants were placed under a selective pressure in vitro *(40)*. Cilgavimab selected for N74K, R346I, K444Q/E/R and S686G, tixagevimab selected for G476D and N487D, and the combination selected for R346G, E484K, and F486V. Unlike sotrovimab and casirivimab-imdevimab, tixagevimab-cilgavimab is administered intramuscularly, which provides lower serum concentrations than when equivalent doses are administered intravenously. In vitro neutralization of BA.1 Omicron was compromised for both tixagevimab and cilgavimab *(41)(42)*, but for subsequent earlier Omicron sublineages, the activity of cilgavimab (but not tixagevimab) was partially restored *(43)*. For more recent variants including BA.2.75.2, BQ.1, BQ.1.1, and XBB lineages, the in vitro neutralization of both antibodies is compromised *(22)(44)(45)(46)(47)*.

Kommentare zur Leitlinie:

Hydrochloroquine ist in Deutschland in diesem AWG derzeit nicht zugelassen.

National COVID-19 Clinical Evidence Taskforce, 2023 [4].

Australian guidelines for the clinical care of people with COVID-19: version 74.1

Zielsetzung/Fragestellung

This guideline aims to provide specific, patient-focused recommendations on management and care of people with suspected or confirmed COVID-19. With the exception of chemoprophylaxis for the prevention of infection in people exposed to COVID -19, the guideline does not include other interventions used in the prevention of COVID-19 infection or transmission. Within each recommendation, the patient population of interest is specified.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: multidisciplinary guideline panels;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: All panel members complete a declaration of potential conflicts of interest, and absent themselves from discussions related to these potential conflicts;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert

Recherche/Suchzeitraum:

- Ständige Aktualisierung – hier zuletzt am 30.05.2023

LoE/GoR

- For systematic reviews, the risk of bias or quality assessment of included studies presented in the review is used where available. For individual primary studies, each study is assessed for risk of bias. Randomised trials are assessed using the Cochrane Risk of Bias 2.0 assessment tool. Non-randomised studies are assessed using the ROBINS-I Risk of Bias assessment tool
- This guideline uses GRADE methodology, which is supported by the online guideline development and publication platform 'MAGICapp' (Making GRADE the Irresistible Choice)
- The following criteria are used in determining the strength of recommendations:
  - Strong for: moderate to high certainty evidence suggests that benefits in critical outcomes clearly outweigh the reported harms; a strong recommendation can be made in the absence of high-certainty evidence if patients are expected to highly desire such practice and there are no potential harms in providing it.
  - Strong against: moderate to high certainty evidence suggests harms outweigh benefits; high certainty evidence suggests lack of benefits.
  - Conditional for: moderate to high certainty evidence suggests equivalent benefits and harms, patients would mostly want to receive the practice, and there is no significant resources implication in doing so; low certainty evidence suggests benefits outweigh harms and there are no significant implications in patients' preferences or resources implications.
  - Conditional against: moderate to high certainty evidence suggests equivalent benefits and harms, but there is expected large variation in patients' preference to receive this practice or important resource implications; low certainty evidence suggests harms outweigh benefits and there are no significant implications in patients' preferences or resource implications.
  - Consensus statement: evidence is absent or of insufficient certainty; unclear balance between benefits and harms, and there is expected large variation in patients'

preferences. No formal method of reaching consensus was used but this was addressed in internal reviews.

Empfehlungen

8. Chemoprophylaxis

Updated

Info Box

The Drug Treatment Panel is responsible for developing recommendations specific to pre- and post-exposure prophylaxis.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

Currently there are no recommended chemoprophylaxis for COVID-19 pre or post-exposure prophylaxis

8.2 Hydroxychloroquine for pre-exposure prophylaxis

Not recommended

For healthcare workers with no active COVID-19, do not use hydroxychloroquine for pre-exposure prophylaxis outside of randomised trials with appropriate ethical approval.

Additional information

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use hydroxychloroquine for pre-exposure prophylaxis in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Important harms

General adult population
In addition to uncertainty around the benefits for people at high risk of being exposed to individuals with COVID-19, there are well-known harms, with potentially severe adverse events. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold. Long-term harms include retinopathy and chronic cardiac myopathy, among several others.

There are several known and potential interactions with other drugs. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses.

Children and adolescents
Paediatricians have considerable experience with hydroxychloroquine in children and adolescents for other indications.

Pregnant and breastfeeding women
Hydroxychloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases. Studies of hydroxychloroquine for these indications have shown a favourable safety profile, though further research is needed.

People requiring palliative care and older people living with frailty or cognitive impairment
There may be additional concerns regarding harms in these populations.

Certainty of the Evidence

Low

General adult population
Certainty of the evidence is low for laboratory-confirmed diagnosis, moderate for adverse events and confirmed or probable infection (due to included studies terminating early), low for serious adverse events and symptoms compatible with COVID-19 (due to studies being terminated early and few events), and very low for discontinuation due to aderse events.

Children and adolescents, pregnant women, people requiring palliative care and older people living with frailty or cognitive impairment
Certainty of the evidence was downgraded further for all outcomes due to indirectness, as these special populations were not included in the trials.

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to take risks.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

Equity

Important issues, or potential issues not investigated

General adult population
We have no systematically collected direct evidence regarding impact on equity. There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit-to-harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
Since these populations are particularly at risk from COVID-19, we encourage trials that include these populations (with appropriate baseline measurement of frailty and cognitive impairment). Given the absence of trials and uncertain benefit-to-harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

Important issues, or potential issues not investigated

General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, hydroxychloroquine is likely to be acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit-to-harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Important issues, or potential issues not investigated

Implementability of the recommendation is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population
There is currently limited evidence about the impact of hydroxychloroquine for pre-exposure prophylaxis on the prevention of COVID-19 in healthcare workers. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that hydroxychloroquine for pre-exposure prophylaxis should only be used to prevent COVID-19 infection in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of once-weekly hydroxychloroquine for pre-exposure prophylaxis for the prevention of COVID-19 infection in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Healthcare workers (with no active or prior COVID-19)
Intervention: Pre-exposure hydroxychloroquine
Comparator: Placebo

Summary

Pre-exposure prophylactic hydroxychloroquine may be no more effective at preventing COVID-19 infection in high-risk healthcare workers than placebo and may result in more adverse events.

What is the evidence informing this recommendation?

Evidence comes from three randomised trials that compared hydroxychloroquine as pre-exposure prophylaxis with placebo in 1884 high-risk healthcare workers with no active or prior COVID-19 *[188][189][394]*.

We have found two new studies comparing hydroxychloroquine as pre-exposure prophylaxis with placebo among healthcare workers at high risk (Syed et al. medRxiv doi: 10.1101/2021.05.17.21257012 and Naggie et al. medRxiv doi: 10.1101/2021.08.19.21262275). These studies are currently under review and will be incorporated in a future version of the guideline.

Study characteristics

Two studies reported comparatively low doses of hydroxychloroquine: in Rajasingham et al. participants were given a loading dose of 400 mg (two 200 mg tablets) of hydroxychloroquine twice separated by 6-8 hours, followed by 400 mg (two 200 mg tablets) either once or twice weekly for 12 weeks *[189]*. Participants in Grau-Pujol et al. were given 400 mg hydroxychloroquine daily for 4 days, followed by 400 mg once weekly for one month *[?]*. In the study by Abella et al. participants received 600 mg of hydroxychloroquine daily for 8 weeks *[188]*.

Median age ranged from 31 to 42 years in the hydroxychloroquine arms and from 34 to 40 years in the placebo arms. The proportion of women ranged from 53% to 83% in the hydroxychloroquine arms and 49% to 73% in the placebo arms. One study explicitly excluded pregnant women *[?]*, one study did not specify whether pregnant or breastfeeding women were eligible *[188]*, and no pregnant women enrolled in the third study, although 30 women reported breastfeeding at baseline *[189]*.

What are the main results?

Pre-exposure prophylactic hydroxychloroquine probably increases incidence of adverse events (108 more per 1000 healthcare workers; RR 1.45 CI 95% 1.14 to 1.84; 1801 participants in 3 studies). Pre-exposure prophylactic hydroxychloroquine may make little or no difference to the number of people who contract laboratory-confirmed COVID-19, experience symptoms compatible with COVID-19, develop confirmed or probable infection, experience serious adverse events or who discontinue treatment due to adverse events.

Our confidence in the results

Certainty of the evidence is low for laboratory-confirmed diagnosis, moderate for adverse events and confirmed or probable infection (due to included studies terminating early), low for serious adverse events and symptoms compatible with COVID-19 (due to studies being terminated early and few events), and very low for discontinuation due to adverse events.

Additional information

According to the Therapeutic Goods Administration, known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiac myopathy [52]. There are several known and potential interactions with other drugs [52]. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses. In **pregnancy**, it is only recommended when benefits outweigh harms [52].

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Pre-exp HCQ	Certainty of the Evidence (Quality of evidence)	Plain language summary
Laboratory-confirmed diagnosis End of treatment 9 Critical	Relative risk 0.87 (CI 95% 0.4 — 1.88) Based on data from 1,877 participants in 3 studies. [1] (Randomized controlled)	**16** per 1000 Difference:	**14** per 1000 **2 fewer per 1000** (CI 95% 10 fewer — 14 more)	**Low** Due to serious risk of bias and serious imprecision [2]	Hydroxychloroquine pre-exposure prophylaxis may have little impact on laboratory-confirmed diagnosis in healthcare workers (26 events).
All-cause mortality End of treatment 6 Important	Based on data from 1,608 participants in 2 studies. [3]				There were no deaths.
Serious adverse events End of treatment 6 Important	Relative risk 0.78 (CI 95% 0.31 — 2.01) Based on data from 1,752 participants in 2 studies. [4] (Randomized controlled)	**11** per 1000 Difference:	**9** per 1000 **2 fewer per 1000** (CI 95% 8 fewer — 11 more)	**Low** Due to serious risk of bias and serious imprecision [5]	Hydroxychloroquine pre-exposure prophylaxis may have little impact on serious adverse events in healthcare workers (18 events).
Adverse events End of treatment 6 Important	Relative risk 1.45 (CI 95% 1.14 — 1.84) Based on data from 1,801 participants in 3 studies. [6] (Randomized controlled)	**241** per 1000 Difference:	**349** per 1000 **108 more per 1000** (CI 95% 34 more — 202 more)	**Moderate** Due to serious risk of bias [7]	Hydroxychloroquine pre-exposure prophylaxis probably increases adverse events in healthcare workers.
Symptoms compatible with COVID-19 12 weeks 6 Important	Relative risk 0.75 (CI 95% 0.5 — 1.11) Based on data from 1,483 participants in 1 studies. [8] (Randomized controlled)	**77** per 1000 Difference:	**58** per 1000 **19 fewer per 1000** (CI 95% 39 fewer — 8 more)	**Low** Due to serious risk of bias and serious imprecision [9]	Hydroxychloroquine pre-exposure prophylaxis may have little impact on development of symptoms compatible with COVID-19 in healthcare workers (95 events).
Confirmed or probable infection 12 weeks 6 Important	Relative risk 0.87 (CI 95% 0.6 — 1.27) Based on data from 1,483 participants in 1 studies. [10] (Randomized controlled)	**79** per 1000 Difference:	**69** per 1000 **10 fewer per 1000** (CI 95% 32 fewer — 21 more)	**Moderate** Due to serious risk of bias [11]	Hydroxychloroquine pre-exposure prophylaxis probably has little or no impact on confirmed or probable infection (107 events).
Discontinuation due to adverse events 8 weeks 6 Important	Relative risk 0.95 (CI 95% 0.2 — 4.54) Based on data from 125 participants in 1 studies. [12] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [13]	There were too few events (6 events) to determine whether hydroxychloroquine pre-exposure prophylaxis increases or decreases discontinuation due to adverse events.

8.4 Tixagevimab plus cilgavimab (Evusheld) for pre-exposure prophylaxis

Consensus recommendation

New

Do not routinely use tixagevimab plus cilgavimab (Evusheld) for pre-exposure prophylaxis of COVID-19.

Additional information

The Taskforce previously recommended that tixagevimab plus cilgavimab (Evusheld) should not be routinely used for pre-exposure prophylaxis, but that use may be considered in individuals who are severely immunocompromised. This recommendation was based on the PROVENT trial [454], in which 5197 unvaccinated adults were administered a single 300 mg dose of Evusheld consisting of two intramuscular injections (150 mg tixagevimab and 150 mg cilgavimab).

The PROVENT trial was conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of tixagevimab plus cilgavimab (Evusheld) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that tixagevimab plus cilgavimab (Evusheld) is effective as pre-exposure prophylaxis due to currently circulating variants of COVID-19; however, use maybe considered in exceptional circumstances, in individuals who are severely immunocompromised where risk of infection with the BA2 variant is more likely, as in vitro evidence suggests that some efficacy remains for Omicron BA2 variant.

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Tixagevimab plus cilgavimab probably has little impact on incidence of positive SARS-CoV-2 infection, emergency department visits, adverse events or serious adverse events. We are unsure if tixagevimab plus cilgavimab impacts all-cause mortality or progression to severe disease.

Certainty of the Evidence

Moderate

Certainty is moderate for positive SARS-CoV-2 infection, emergency department visits, adverse events and serious adverse events due to serious imprecision (reliance on a single study). Certainty is low for all-cause mortality and progression to severe disease due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values.

Resources

Important issues, or potential issues not investigated

The limited availability of tixagevimab plus cilgavimab, as well as the high cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of tixagevimab plus cilgavimab may affect equity based on geographic area and access to tixagevimab plus cilgavimab.

Acceptability

Important issues, or potential issues not investigated

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

Feasibility

No important issues with the recommended alternative

The Therapeutic Goods Administration provisionally approved the use of tixagevimab plus cilgavimab for use as pre-exposure prophylaxis on 24 February 2022 for the following indications:

- individuals who have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments that make it likely that they will not mount an adequate immune response to COVID-19 vaccination; or
- individuals for whom vaccination is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or COVID-19 vaccine component (TGA).

Clinical Question/ PICO

Population: Evusheld for COVID-19 prophylaxis
Intervention: Evusheld
Comparator: Placebo – pre-exposure prophylaxis

Summary

Evidence indicates that tixagevimab plus cilgavimab likely has little impact in reducing SARS-CoV-2 infection when used as pre-exposure prophylaxis, however it may be of benefit in treating patients who are severely immunocompromised.

What is the evidence informing this recommendation?
Evidence comes from the PROVENT trial *[454]* that compared tixagevimab plus cilgavimab (Evusheld) with placebo in 5197 adults who were expected to benefit from having received treatment due to either increased risk of inadequate response to vaccination, or increased risk of exposure due to a high density work and/or living environment.

Study characteristics
Mean age of participants was 53 years and 46% were women. Approximately 25% of participants were aged 65 years or over. Participants received a single dose of Evusheld, consisting of two simultaneous intramuscular injections (150 mg tixagevimab and 150 mg cilgavimab). Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?
Tixagevimab plus cilgavimab probably has little impact on incidence of positive SARS-CoV-2 infection, emergency department visits, adverse events or serious adverse events. We are unsure if tixagevimab plus cilgavimab impacts all-cause mortality or progression to severe disease.

Our confidence in the results
Certainty of the evidence is moderate for positive SARS-CoV-2 infection, emergency department visits, adverse events and serious adverse events due to serious imprecision (reliance on a single study). Certainty is low for all-cause mortality and progression to severe disease due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration has granted provisional determination for Evusheld. As of 24 February 2022,

Evusheld is not approved for use for the prevention of SARS-CoV-2 infection.

Outcome Timeframe	Study results and measurements	Comparator Placebo – pre-exp prophylaxis	Intervention Evusheld	Certainty of the Evidence (Quality of evidence)	Plain language summary
Positive SARS-CoV-2 infection 9 Critical	Relative risk 0.24 (CI 95% 0.1 — 0.55) Based on data from 5,172 participants in 1 studies. [1] (Randomized controlled)	10 per 1000 Difference:	2 per 1000 **8 fewer per 1000** (CI 95% 9 fewer — 4 fewer)	Moderate Due to serious imprecision [2]	Evusheld probably has little impact on positive SARS-CoV-2 infection (25 events)
Severe COVID-19 6 Important	Relative risk 0.17 (CI 95% 0.01 — 4.12) Based on data from 5,172 participants in 1 studies. [3] (Randomized controlled)	1 per 1000 Difference:	0 per 1000 **1 fewer per 1000** (CI 95% 1 fewer — 3 more)	Low Due to very serious imprecision [4]	We are uncertain whether evusheld increases or decreases severe COVID-19 (1 event)
Emergency department visits 6 Important	Relative risk 1.54 (CI 95% 0.92 — 2.57) Based on data from 5,172 participants in 1 studies. [5] (Randomized controlled)	11 per 1000 Difference:	17 per 1000 **6 more per 1000** (CI 95% 1 fewer — 17 more)	Moderate Due to serious imprecision [6]	Evusheld probably has little or no difference on emergency department visits (77 events)
Adverse events 6 Important	Relative risk 1.03 (CI 95% 0.95 — 1.12) Based on data from 5,197 participants in 1 studies. [7] (Randomized controlled)	342 per 1000 Difference:	352 per 1000 **10 more per 1000** (CI 95% 17 fewer — 41 more)	Moderate Due to serious imprecision [8]	Evusheld probably has little or no difference on adverse events
Serious adverse events 6 Important	Relative risk 1.09 (CI 95% 0.67 — 1.78) Based on data from 5,197 participants in 1 studies. [9] (Randomized controlled)	13 per 1000 Difference:	14 per 1000 **1 more per 1000** (CI 95% 4 fewer — 10 more)	Moderate Due to serious imprecision [10]	Evusheld probably has little or no difference on serious adverse events (73 events)
All-cause mortality 9 Critical	Relative risk 0.5 (CI 95% 0.13 — 2) Based on data from 5,197 participants in 1 studies. [11] (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 2 more)	Low Due to very serious imprecision [12]	We are uncertain whether evusheld increases or decreases all-cause mortality (8 events)

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2023) am 17.10.2023

#	Suchfrage
#1	[mh "COVID-19"]
#2	[mh "SARS-CoV-2"]
#3	(Covid* OR 2019ncov OR cov2 OR ncov19 OR sarscov* OR (ncov* NEAR/3 2019) OR (ncov* NEAR/3 19)):ti,ab,kw
#4	(coronavir* OR (corona NEXT vir*) OR betacoronavir* OR (beta NEXT coronavir*) OR SARS*):ti,ab,kw
#5	((cov*) NEAR/3 (novel OR new OR 2019 OR 19 OR infection* OR disease* OR wuhan OR pneumonia* OR pneumonitis)):ti,ab,kw
#6	(wuhan AND (virus* OR viral OR viridae OR pneumonia* OR pneumonitis)):ti,ab,kw
#7	("Severe Acute Respiratory Syndrome" OR "Severe Acute Respiratory Syndromes" OR "sudden acute respiratory syndrome" OR "severe acute respiratory infection" OR "severe acute respiratory infections" OR SARI):ti,ab,kw
#8	{OR #1-#7}
#9	#8 with Cochrane Library publication date Between Oct 2018 and Oct 2023, in Cochrane Reviews

Systematic Reviews in PubMed am 13.10.2023

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	"COVID-19/prevention and control"[MeSH Major Topic]
2	COVID-19[MeSH Terms] OR SARS-CoV-2[MeSH Terms]
3	Covid*[ti] OR 2019ncov[ti] OR cov2[ti] OR ncov19[ti] OR sarscov*[ti] OR (ncov*[ti] AND 2019[ti]) OR (ncov*[ti] AND 19[ti])
4	Coronavir*[ti] OR corona vir*[ti] OR betacoronavir*[ti] OR beta coronavir*[ti] OR SARS*[ti]
5	(cov[ti]) AND (novel[ti] OR new[ti] OR 2019[ti] OR 19[ti] OR infection*[ti] OR disease*[ti] OR wuhan[ti] OR pneumonia*[ti] OR pneumonitis[ti])
6	(wuhan[tiab]) AND (virus*[ti] OR viral[ti] OR viridae[ti] OR pneumonia*[ti] OR pneumonitis[ti])
7	(("Severe Acute Respiratory Syndrome"[ti] OR "Severe Acute Respiratory Syndromes"[ti] OR "sudden acute respiratory syndrome"[ti]) AND "2"[ti]) OR

#	Suchfrage
	"severe acute respiratory infection"[ti] OR "severe acute respiratory infections"[ti] OR SARI[ti]
8	#2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(prevent*[ti] OR control*[ti] OR precaution*[ti] OR prophylax*[tiab] OR prophylactic[tiab] OR Pre-Exposure[tiab] OR Preexposure[tiab] OR postexposure[tiab] OR post-exposure[tiab] OR exposed[ti] OR Chemoprevent*[tiab] OR Chemoprophylax*[tiab] OR Chemo-prevent*[tiab] OR Chemo-prophylax*[tiab] OR asymptomatic infection*[tiab] OR Inapparent Infection*[tiab] OR subclinical Infection*[tiab] OR presymptomatic infection*[tiab] OR pre-symptomatic infection*[tiab] OR asymptomatic[ti] OR presymptomatic[ti] OR pre-symptomatic[ti] OR Post-Exposure Prophylaxis[mh] OR Pre-Exposure Prophylaxis[mh] OR Chemoprevention[mh] OR infection control[majr] OR Universal Precautions[majr] OR Asymptomatic Infections[mh])
10	((therap*[ti]) AND (globulin*[ti] OR serum*[ti] OR sero*[ti] OR immunoglobulin*[ti])) OR (Antibod*[tiab] AND transfer*[tiab]) OR serotherap*[ti] OR immunotherap*[ti] OR immunization*[ti] OR passive immunization[majr]
11	#9 OR #10
12	#8 AND #11
13	#1 OR #12
14	(#13) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
15	(#14) AND ("2018/10/01"[PDAT] : "3000"[PDAT])

#	Suchfrage
16	(#15) NOT "The Cochrane database of systematic reviews"[Journal]
17	(#16) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 13.10.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"COVID-19/prevention and control"[MeSH Major Topic]
2	COVID-19[MeSH Terms] OR SARS-CoV-2[MeSH Terms]
3	Covid*[ti] OR 2019ncov[ti] OR cov2[ti] OR ncov19[ti] OR sarscov*[ti] OR (ncov*[ti] AND 2019[ti]) OR (ncov*[ti] AND 19[ti])
4	Coronavir*[ti] OR corona vir*[ti] OR betacoronavir*[ti] OR beta coronavir*[ti] OR SARS*[ti]
5	(cov[ti]) AND (novel[ti] OR new[ti] OR 2019[ti] OR 19[ti] OR infection*[ti] OR disease*[ti] OR wuhan[ti] OR pneumonia*[ti] OR pneumonitis[ti])
6	(wuhan[tiab]) AND (virus*[ti] OR viral[ti] OR viridae[ti] OR pneumonia*[ti] OR pneumonitis[ti])
7	(("Severe Acute Respiratory Syndrome"[ti] OR "Severe Acute Respiratory Syndromes"[ti] OR "sudden acute respiratory syndrome"[ti]) AND "2"[ti]) OR "severe acute respiratory infection"[ti] OR "severe acute respiratory infections"[ti] OR SARI[ti]
8	#2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(prevent*[ti] OR control*[ti] OR precaution*[ti] OR prophylax*[tiab] OR prophylactic[tiab] OR Pre-Exposure[tiab] OR Preexposure[tiab] OR postexposure[tiab] OR post-exposure[tiab] OR exposed[ti] OR Chemoprevent*[tiab] OR Chemoprophylax*[tiab] OR Chemo-prevent*[tiab] OR Chemo-prophylax*[tiab] OR asymptomatic infection*[tiab] OR Inapparent Infection*[tiab] OR subclinical Infection*[tiab] OR presymptomatic infection*[tiab] OR pre-symptomatic infection*[tiab] OR asymptomatic[ti] OR presymptomatic[ti] OR pre-symptomatic[ti] OR Post-Exposure Prophylaxis[mh] OR Pre-Exposure Prophylaxis[mh] OR Chemoprevention[mh] OR infection control[majr] OR Universal Precautions[majr] OR Asymptomatic Infections[mh])
10	((therap*[ti]) AND (globulin*[ti] OR serum*[ti] OR sero*[ti] OR immunoglobulin*[ti])) OR (Antibod*[tiab] AND transfer*[tiab]) OR serotherap*[ti] OR immunotherap*[ti] OR immunization*[ti] OR passive immunization[majr]
11	#9 OR #10
12	#8 AND #11
13	#1 OR #12

#	Suchfrage
14	(#13) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp])
15	(#14) AND ("2018/10/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.10.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Anhang

Anhang 1: Hirsch C et al., 2022 [2]

Summary of findings 1. Tixagevimab/cilgavimab compared to placebo for pre-exposure prophylaxis of COVID-19

Tixagevimab/cilgavimab compared to placebo in previously uninfected and unvaccinated people with increased risk of exposure to SARS-CoV-2 or increased risk for inadequate immune response to vaccination, or both

Patient or population: SARS-CoV-2 uninfected people without defined exposure, or with potential exposure to SARS-CoV-2**Setting:** preventive measures

Intervention: tixagevimab/cilgavimab

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty in the evidence (GRADE)	Comments
	Risk with placebo	Risk with tixagevimab/ cilgavimab				
Infection with SARS-CoV-2 within 6 months	27 per 1000	**12 per 1000** (8 to 19)	**RR 0.45** (0.29 to 0.70)	4685 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	Tixagevimab/cilgavimab probably decrease infection with SARS-CoV-2 within 6 months. Participants were censored at unblinding or vaccination. Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta. Extended follow-up data cut-off was 29 August 2021.
Development of clinical COVID-19 symptoms within 6 months	18 per 1000	**3 per 1000** (2 to 6)	**RR 0.18** (0.09 to 0.35)	5172 (1 RCT)	⊕⊕⊕⊕ **High**	Tixagevimab/cilgavimab decrease development of clinical symptoms within 6 months. Participants were censored at unblinding or vaccination. Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta. Extended follow-up data cut-off was 29 August 2021.
All-cause mortality within 6 months[b]	4 per 1000	**3 per 1000** (1 to 7)	**RR 0.64** (0.24 to 1.73)	5197 (1 RCT)	⊕⊕⊖⊖ **Low**[c,d]	Tixagevimab/cilgavimab may result in little to no difference on mortality within 6 months in participants regardless of RT-PCR SARS-CoV-2 status at baseline.

						Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta. Extended follow-up data cut-off was 29 August 2021.
Admission to hospital within 6 months[b]	4 per 1000	**0 per 1000** (0 to 2)	**RR 0.03** (0.00 to 0.59)	5197 (1 RCT/)	⊕⊕⊖⊖ **Low**[e]	Tixagevimab/cilgavimab may decrease admission to hospital within 6 months in participants regardless of RT-PCR SARS-CoV-2 status at baseline. Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta. Extended follow-up data cut-off was 29 August 2021.
Quality of life at longest follow-up	—	—	—	—	—	We identified no studies reporting quality of life.
Adverse events: grade 1 to 2	—	—	—	—	—	We identified no studies reporting grade 1 to 2 adverse events.
Adverse events: grade 3 to 4 within 6 months	—	—	—	—	—	We identified no studies reporting grade 3 to 4 adverse events.
Adverse events: all grade within 6 months[b]	455 per 1000	**455 per 1000** (428 to 487)	**RR 1.00** (0.94 to 1.07)	5197 (1 RCT)	⊕⊕⊖⊖ **Low**[f]	Tixagevimab/cilgavimab may result in little to no difference on the occurrence of all-grade adverse events within 6 months in participants regardless of RT-PCR SARS-CoV-2 status at baseline. Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta. Extended follow-up data cut-off was 29 August 2021.
Serious adverse events within 6 months[b]	33 per 1000	**37 per 1000** (28 to 51)	**RR 1.12** (0.83 to 1.52)	5197 (1 RCT)	⊕⊕⊖⊖ **Low**[g]	Tixagevimab/cilgavimab may result in little to no difference on the occurrence of serious adverse events within 6 months in participants regardless of RT-PCR SARS-CoV-2 status at baseline. Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta. Extended follow-up data cut-off was 29 August 2021.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

CI: confidence interval; **mAb:** monoclonal antibody; **RCT:** randomised controlled trial; **RR:** risk ratio; **RT-PCR:** reverse transcription polymerase chain reaction; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for serious risk of bias (missing outcome data and potentially selection of the reported result).
[b]The safety population included participants with negative, positive and unknown RT-PCR SARS-CoV-2 status at baseline.
[c]Downgraded two levels for very serious imprecision, because of very low number of events and wide confidence intervals.
[d]We did not downgrade for serious risk of bias (measurement of the outcome) because for this outcome it is irrelevant whether participants were aware of the intervention received, and the number of people vaccinated was comparable in both arms.
[e]Downgraded two levels for very serious imprecision because of very low number of events.
[f]Downgraded one level for serious imprecision, because sample size did not meet optimal information size (6,435,640 participants) and one level for serious risk of bias (measurement of the outcome and potentially selection of the reported result).
[g]Downgraded one level for serious imprecision, because sample size did not meet optimal information size (55,674 participants) and one level for serious risk of bias (measurement of the outcome and potentially selection of the reported result).

Summary of findings 2. Casirivimab/imdevimab compared to placebo for pre-exposure prophylaxis of COVID-19

Casirivimab/imdevimab compared to placebo in previously uninfected and unvaccinated people

Patient or population: SARS-CoV-2 uninfected people without defined exposure, or with potential exposure to SARS-CoV-2

Setting: preventive measures

Intervention: casirivimab/imdevimab

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty in the evidence (GRADE)	Comments
	Risk with placebo	Risk with casiriv-				

		imab/imde-vimab				
Infection with-SARS-CoV-2 within 6 months[a]	96 per 1000	**1 per 1000** (0 to 13)	**RR 0.01** (0.00 to 0.14)	825 (1 RCT)	⊕⊕◯◯ **Low**[b,c]	Casirivimab/imdevimab may decrease infection with SARS-CoV-2 within 6 months in participants SARS-CoV-2 antibody seronegative at baseline. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta.
Development of clinical COV-ID-19 symptoms within 6 months	42 per 1000	**1 per 1000** (0 to 11)	**RR 0.02** (0.00 to 0.27)	969 (1 RCT)	⊕⊕◯◯ **Low**[b,c]	Casirivimab/imdevimab may decrease development of clinical COVID-19 symptoms within 6 months. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta.
All-cause mor-tality within 6 months	1 study reported mortality by week 24. There were no deaths.		**Not estimable**	969 (1 RCT)	⊕◯◯◯ **Very low**[b,d]	The evidence is very uncertain about the effect of casirivimab/imdevimab on mortality. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta.
Admission to hospital within 6 months	—		—	—	—	We identified no studies reporting admission to hospi-tal.
Quality of life at longest follow-up	—		—	—	—	We identified no studies reporting quality of life.
Adverse events: grade 1 to 2	—		—	—	—	We identified no studies reporting grade 1 to 2 adverse events.
Adverse events: grade 3 to 4 with-in 6 months	13 per 1000	**6 per 1000** (1 to 24)	**RR 0.44** (0.10 to 1.95)	969 (1 RCT)	⊕◯◯◯ **Very low**[b,e]	The evidence is very uncertain about the effect of casirivimab/imdevimab on the occurrence of grade 3 to 4 adverse events within 6 months. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta.
Adverse events: all grades within 6 months	483 per 1000	**551 per 1000** (474 to 633)	**RR 1.14** (0.98 to 1.31)	969 (1 RCT)	⊕⊕◯◯ **Low**[b,f]	Casirivimab/imdevimab may increase the occurrence of all-grade adverse events within 6 months slightly. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta.

Serious adverse events within 6 months	8 per 1000	**7 per 1000** (1 to 35)	**RR 0.82** (0.16 to 4.21)	969 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,e]	The evidence is very uncertain about the effect of casirivimab/imdevimab on the occurrence of serious adverse events within 6 months. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

CI: confidence interval; **mAb:** monoclonal antibody; **RCT:** randomised controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The outcome was assessed in participants SARS-CoV-2 antibody seronegative at baseline.
[b]Downgraded one level for serious risk of bias (missing information regarding randomisation process and allocation concealment).
[c]Downgraded one level for serious imprecision, because of low number of events.
[d]Downgraded two levels for very serious imprecision, because there were no events, effect not estimable.
[e]Downgraded two levels for very serious imprecision, because of very low number of events and very wide confidence intervals.
[f]Downgraded one level for very serious imprecision, because of wide confidence intervals.

Anhang 2: Soeroto AY et al., 2022 [5].

TABLE 1 Characteristics of included studies

Study	Design	Participants	Tixagevimab-cilgavimab dose	Control	Predominant SARS-CoV-2 variant	Mean age (years)	Male (%)	Adverse events	Outcome[a]
Al Jurdi A et al.[28] 2022	Retrospective cohort	Solid organ (kidney, liver, and lung) transplant recipients	222 patients: - 150-150 mg IM (40.5%) - 300-300 mg IM (59%) - 450-450 mg IM (0.5%)	222 patients:	Omicron BA.1 and BA.2	64	61%	- Nausea, vomiting, diarrhea (1.8%) - Headache (1.4%) - Abdominal pain (0.9%)	1,2,4
Bertrand D et al.[26] 2022	Retrospective cohort	Fully vaccinated kidney transplant recipients with no or weak humoral response (<264 BAU/ml) 1 months after last injection	412 patients: 150 mg tixagevimab + 150 mg cilgavimab IM	160 patients: - SOC (61.3%) - Casirivimab-imdevimab (38.7%)	Omicron BA.1 and BA.2	59.6	60.6%	No serious adverse events (Details not reported)	1,2,3,4
Kaminski H et al.[27] 2022	Retrospective cohort	Kidney transplant recipients, considered as nonresponders (anti-spike antibody <7 BAU/ml) or low responders (anti-spike antibody 7–264 BAU/ml) after 3 doses of mRNA vaccines	333 patients: 150 mg tixagevimab + 150 mg cilgavimab IM	97 patients: SOC only	Omicron BA.1 and BA.2	59.6	62%	Not reported	1,2,3,4
Kertes J et al.[28] 2022	Retrospective cohort	Patients aged >12 years with minimum weight of 40 kg, who did not have positive PCR or antigen results in the last months, were not vaccinated against COVID-19 in the last 2 weeks, and had evidence of severe immunosuppression	825 patients: 150 mg tixagevimab + 150 mg cilgavimab IM	4299 patients: SOC only	Omicron BA.1 and BA.2	61.3	54.7%	Not reported	1,2,3,4
Levin MJ et al.[16] 2022	Double-blind RCT	Adults (>18 years) who had an increased risk of an inadequate response to COVID-19 vaccination, an increased risk of exposure to SARS-CoV-2, or both	3441 patients: 150 mg tixagevimab + 150 mg cilgavimab IM	1731 patients: placebo	B.1.1.7_1 (Alpha) and B.1.617.2 (Delta)	53.5	53.9%	- Injection site reaction (2.7%) - Anaphylaxis (<0.1%)	1,3
Young-Xu et al.[29] 2022	Retrospective cohort	Patients aged >18 years who were immunocompromised	1733 patients: 300 mg tixagevimab + 300 mg cilgavimab IM	6354 patients: SOC only	Omicron BA.1, BA.2, and BA.2.12.1	67.9	91%	Not mentioned	1,2,4

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-269

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) Bundesärztekammer, Dezernat 1 – Ärztliche Versorgung und Arzneimittel, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	7. November 2023

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Präexpositionsprophylaxe einer Coronavirus-19-Erkrankung (coronavirus disease 2019, COVID-19) bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Zur Präexpositionsprophylaxe (PreP) von COVID-19 bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht hat in Deutschland lediglich das monoklonale Antikörper-Kombinationspräparat Tixagevimab/Cilgavimab (Evusheld®) eine Zulassung erhalten. Die Zulassung datiert vom 25.03.2022. Die Anwendung als PreP beinhaltet zwei intramuskuläre Injektionen der beiden Antikörper, die bei fortbestehender Indikation halbjährlich vorzunehmen sind (1). Die Zulassung begründete sich auf den Daten der PROVENT-Studie, einer randomisierten placebokontrollierten Studie, die eine 82,8-prozentige Risikoreduktion bezüglich des Auftretens einer symptomatischen Infektion bei Patientinnen und Patienten mit Risikofaktoren für einen schweren COVID-19-Verlauf (95 % CI 65,8–91,4), Follow-up 6 Monate) in der Anwendung als PreP aufzeigen konnte (2). Im Studienzeitraum zirkulierten neben dem Wildtyp die Alpha-, Beta- und Delta-Variante. Unter Federführung der Deutschen Gesellschaft für Infektiologie (DGI) erfolgte im Mai 2022 die Erstellung der S1-Leitlinie zur „SARS-CoV-2 Prä-Expositionsprophylaxe“, in der Indikationsstellung und Anwendung klar definiert wurden (3). Auch die STIKO griff in ihrer „21. Aktualisierung der COVID-19-Impfempfehlung“ eine Empfehlung und wissenschaftliche Begründung zur COVID-19-PreP mit Tixagevimab/Cilgavimab für bestimmte Personengruppen (relevanten Beeinträchtigung der Immunabwehr, Personen mit nachgewiesener fehlender Serokonversion nach COVID-19-Impfung sowie Personen mit Kontraindikationen gegen die zugelassenen COVID-19-Impfstoffe) auf.

Seit Einsatz jeglicher monoklonaler Antikörper gegen COVID-19 ist jedoch bereits bekannt, dass die neutralisierende Wirksamkeit der Präparate gegen verschiedene Sars-CoV-2-Varianten und deren Sublinien stark variabel ist. Ebenso bekannt ist die genetische Variabilität von Sars-CoV-2, die dazu führt, dass sich stets verändernde Virusvarianten weltweit zirkulieren und vorherrschend sind. Diese steten Veränderungen von Sars-CoV-2 und die Tatsache, dass die Neutralisationskapazität der monoklonalen Antikörper stark von der Virusvariante und den Sublinien abhängig ist, führte bereits im Dezember 2022 dazu, dass die Europäische Arzneimittel-Agentur (EMA) auf die fehlende oder reduzierte In-vitro-Wirksamkeit der zugelassenen monoklonalen Antikörper gegenüber den zu diesem Zeitpunkt bereits vorherrschenden Sublinien der Omikron-Variante hingewiesen hat (4). Verschiedene publizierte In-vitro-Studien zeigten eine fehlende Neutralisationskapazität gegen Sublinien von Sars-CoV-2-Omikron-Variante BA.5 (BQ1.1, BF.7 und BQ.1) sowie gegen die XBB- und XBB.1-Sublinien (5-8). Klinische Wirksamkeitsdaten liegen somit weiterhin nicht vor.

Unter Berücksichtigung der dynamischen Datenlage erfolgte im Februar 2023 eine Aktualisierung der Empfehlung zur Sars-CoV-2-PreP mit Tixagevimab/Cilgavimab, die den Einsatz der Antikörperkombination deutlich eingrenzte. Seither soll eine PreP nur noch in begründeten Einzelfällen bei bestimmten Hochrisikopersonen zum Einsatz kommen (9).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Die protektive Wirkung der PreP mit Tixagevimab/Cilgavimab wird in Fachkreisen nur noch als geringgradig eingeschätzt.

Bei hohem Risiko für schwere Verläufe kann die Gabe des Kombinationsantikörpers in begründeten Einzelfällen jedoch als additive Gabe weiterhin in Erwägung gezogen werden. Wenn Tixagevimab/Cilgavimab zur SARS-CoV-2-PreP eingesetzt wird, empfiehlt die STIKO eine Dosierung von 300 mg/300 mg ab einem Alter von zwölf Jahren und einem Körpergewicht von mindestens 40 kg (10) – also eine Dosierung, die nicht der Zulassung entspricht (laut Fachinformation beträgt die empfohlene Dosierung hier 150 mg/150 mg).

Unter begründeten Einzelfällen werden Hochrisikopersonen mit schwerer Immundefizienz und einer erwartbaren oder nachgewiesenen starken Einschränkung der Immunantwort auf die COVID-19-Impfung verstanden. Dies sind insbesondere Personen:

- nach autologer oder allogener Stammzelltransplantation vor immunologischer Rekonstitution.
- unter oder nach Therapie mit Anti-B-Zell-Antikörpern, wenn keine Rekonstitution der B-Zell-Kapazitäten erfolgt ist.
- unter CAR-T-Zell-Therapie.
- unter starker Immunsuppression, z. B. nach Transplantation eines soliden Organs oder unter laufender Chemotherapie.
- mit genetisch bedingten Immundefekten, die die antivirale Immunität beeinträchtigen.

Falls keine PreP vorgenommen wird, ist unabhängig davon die Beachtung von Hygienemaßnahmen und vor allem die COVID-19-Impfung als wesentliche Maßnahme für jegliche Risikopersonen sinnvoll und empfohlen (9).
Im Falle einer Sars-CoV-2-Infektion o. g. Personengruppen sei an dieser Stelle auf die Möglichkeit und die Empfehlungen einer frühzeitigen antiviralen Therapie hingewiesen (11, 12).

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