Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Tixagevimab/ cilgavimab (first dossier requirement: COVID-19, increased risk of severe course, ≥ 12 years)

of 20 April 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient tixagevimab/ cilgavimab (Evusheld) was listed for the first time on 15 June 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 16 September 2022, tixagevimab/ cilgavimab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7) and thus, subject to first dossier requirement according to Chapter 5 Section 1, paragraph 2, number 4.

On 14 October 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 3 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient tixagevimab/ cilgavimab with the new therapeutic indication indication "treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19" in due time (at the latest within

four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 January 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of tixagevimab/ cilgavimab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of tixagevimab/ cilgavimab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Tixagevimab/ cilgavimab (Evusheld) according to the product information

EVUSHELD is indicated for the treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Therapeutic indication of the resolution (resolution of 6 April 2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with COVID-19 disease who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which tixagevimab/ cilgavimab has a considerably reduced or no sufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

b) Adults with COVID-19 who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which tixagevimab/ cilgavimab has sufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

c) Adolescents aged 12 to < 18 years weighing at least 40 kg with COVID-19 who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19

Appropriate comparator therapy:

Therapy according to doctor's instructions

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO:

on 1. Besides tixagevimab/ cilgavimab, the active ingredients casirivimab/ imdevimab, regdanvimab, remdesivir, nirmatrelvir/ ritonavir and sotrovimab are approved for the treatment of COVID-19 in patients who do not require supplemental oxygen therapy and who are at increased risk of progressing to severe COVID-19.

on 2. In the therapeutic indication of COVID-19 disease, without the need for supplemental oxygen and with an increased risk of progressing to severe COVID-19, no non-medicinal treatments are indicated.

on 3. Resolutions on the benefit assessment of remdesivir according to Section 35a SGB V of 16 September 2021 and 7 July 2022.

Resolution on the benefit assessment of casirivimab/ imdevimab according to Section 35a SGB V of 6 October 2022.

Resolution on the benefit assessment of sotrovimab according to Section 35a SGB V of 3 November 2022.

Resolution on the benefit assessment of nirmatrelvir/ ritonavir according to Section 35a SGB V of 15 December 2022.

on 4. The generally recognised state of medical knowledge on which the resolution of the G-BA is based, was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

At present, the treatment of COVID-19 is based on the clinical severity (mild, severe) with the predominant symptoms. A predominant percentage of adults with mild to moderate, symptomatic COVID-19 can be managed as outpatients. Specific therapeutic measures are usually not required for mildly to moderately symptomatic COVID-19. For subjects in outpatient care, supportive measures may include, e.g. analgesics or antipyretics and, for elderly and/or previously ill patients, thromboembolism prophylaxis if necessary.

The active ingredients remdesivir, casirivimab/ imdevimab, sotrovimab and nirmatrelvir/ ritonavir were assessed by the G-BA as part of the early benefit assessment.

For remdesivir, a hint for a minor additional benefit was identified in adults with COVID-19 who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19. So far, there is only limited experience with this active ingredient in care, which is why the significance cannot yet be conclusively assessed. Therefore, remdesivir is not determined to be appropriate comparator therapy for the present patient groups.

A hint for a considerable additional benefit of casirivimab/ imdevimab and sotrovimab was identified for the treatment of adult patients with COVID-19, who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, and who are infected with a viral variant against which the active ingredients show sufficient efficacy. The viral variants against which casirivimab/ imdevimab or sotrovimab show sufficient efficacy are currently no longer circulating. For casirivimab/ imdevimab, no sufficient efficacy could be demonstrated against the currently dominant variants of the Omicron virus using in vitro neutralisation tests. For sotrovimab, only a significantly reduced efficacy could be demonstrated against the currently dominant variants of the Omicron virus using in vitro neutralisation tests. Consequently, the G-BA was unable to identify an additional benefit for patients with COVID-19 due to infection with a viral variant against which the active ingredients do not show sufficient efficacy. Therefore, neither casirivimab/ imdevimab nor sotrovimab is determined to be an appropriate comparator therapy for tixagevimab/ cilgavimab at this time.

For nirmatrelvir/ ritonavir, a hint for a considerable additional benefit. was identified in adults with COVID-19 who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19. So far, there is only limited experience with this

active ingredient in care, which is why the significance cannot be conclusively assessed. Therefore, nirmatrelvir/ ritonavir is not determined to be the appropriate comparator therapy for the present patient groups.

Moreover, the active ingredient regdanvimab has been approved for the treatment of COVID-19 patients who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19. Regardless of the clinical relevance, regdanvimab is not currently available in Germany and therefore does not represent a component of the specific appropriate comparator therapy.

As the disease progresses, symptoms may deteriorate and hospitalisation may be indicated due to COVID-19. This treatment setting is no longer addressed by the present therapeutic indication for starting treatment with tixagevimab/ cilgavimab. In these cases, especially with severe organ dysfunction (lung, kidney), intensive care intervention may also be necessary. For adults with more severe courses of the disease who require hospitalisation due to COVID-19, supportive measures may include early oxygen administration or, in the case of severe respiratory impairment, mechanical ventilation as well as thrombosis prophylaxis or therapeutic anticoagulation and balanced fluid therapy, depending on the previous and concomitant diseases. Prevention of secondary infections and sepsis therapy in accordance with guidelines should be provided.

According to the S3 guideline on inpatient therapy of patients with COVID-19, therapy with dexamethasone should be given to patients on low/ high flow oxygen therapy or non-invasive/ invasive ventilation. As this concerns later treatment settings, it is not included in the appropriate comparator therapy derived for the present therapeutic indication.

In the overall assessment of the evidence and clinical practice, the G-BA currently considers a therapy according to the doctor's instructions to be an appropriate comparator therapy for tixagevimab/ cilgavimab for all patient populations to be assessed. Therapy, according to doctor's instructions, is understood to be the therapy that ensures the best possible, patient-individually optimised treatment of COVID-19. In the therapy according to doctor's instructions, depending on the severity of the disease, primary symptomatic medicinal therapies (e.g. analgesics, antipyretics, thrombosis prophylaxis) should be taken into account in the treatment of non-hospitalised patients, if indicated. These therapies can also be used during therapy with tixagevimab/ cilgavimab.

If the disease progresses and the patients are hospitalised, further medicinal therapies (e.g. dexamethasone, anticoagulation/ thrombosis prophylaxis, antibiotics) as well as non-medicinal therapies (e.g. oxygen administration, type of ventilation, balanced fluid therapy) must be taken into account in both the intervention arm and the control arm.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment order.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of tixagevimab/ cilgavimab is assessed as follows:

a) Adults with COVID-19 disease who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which tixagevimab/ cilgavimab has a considerably reduced or no sufficient efficacy

   For the treatment of adult patients with COVID-19 disease who do not require supplemental oxygen therapy, are at increased risk of progressing to severe COVID-19, and are infected with a viral variant against which tixagevimab/ cilgavimab shows a considerably reduced or no sufficient efficacy, the additional benefit is not proven.

Justification:

The study data of the TACKLE study [for the study description, see patient population b)] show that approx. 38% of the patients for whom corresponding sequencing data were available were infected with the alpha variant. Other frequently detected variants were B.1.1.519 (19%), gamma (12%) and delta (10%). The currently predominant variants of the Omicron virus were not detected among the study participants. According to the product information, tixagevimab/ cilgavimab shows antiviral activity in vitro against Omicron variant BA.2, while Omicron variants BA.1, BA.1.1, BA.4 and BA.5 show reduced sensitivity to tixagevimab/ cilgavimab. In addition, there is no neutralization activity in vitro against the other sublines BQ.1/BQ.1.1, BA.4.6, BF.7. XBB, according to information from the specialist group for intensive care medicine, infectious diseases and emergency medicine (COVRIIN) at the Robert Koch Institute (RKI)[2].

Tixagevimab/ cilgavimab therefore shows a considerably reduced or no efficacy regarding the Omicron viral variants circulating in Germany at the time of the resolution (BA.2.75; BA.5; XBB.1 and respective sublines) (proven using in vitro neutralisation tests). Due to this considerably reduced or no efficacy, the effects observed in the TACKLE study are not transferable to patients infected with the Omicron viral variants circulating at the time of the benefit assessment.

In the TACKLE study, only patients infected with viral variants for which there was sufficient neutralisation activity were examined. Consequently, on the basis of the TACKLE study, it is only possible to make statements on the additional benefit for patients who are infected with a viral variant for which there is sufficient neutralisation activity.

Therefore, for adults infected with a viral variant of SARS-CoV-2 for which there is significantly reduced or insufficient neutralisation activity of tixagevimab/ cilgavimab based on evidence or current pandemic activity (currently variants of the Omicron virus), no statement on the additional benefit of treating COVID-19 with tixagevimab/ cilgavimab is possible. For this patient population (patient population a), an additional benefit of tixagevimab/ cilgavimab compared to the appropriate comparator therapy is not proven.

[2] COVRIIN specialist group: Antiviral therapy in the early phase of SARS-CoV-2 infection [last revised: 27.01.2023; last accessed 02.03.2023]

b) Adults with COVID-19 who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which tixagevimab/ cilgavimab has sufficient efficacy

For the treatment of adult patients with COVID-19 disease who do not require oxygen therapy, who are at increased risk of severe COVID-19, and who are infected with a viral variant against which tixagevimab/ cilgavimab has sufficient efficacy, there is a hint for a minor additional benefit of tixagevimab/ cilgavimab compared to the appropriate comparator therapy.

Justification:

For the benefit assessment, the pharmaceutical company submits the TACKLE study.

The TACKLE study is an ongoing, double-blind, randomised controlled trial comparing treatment with tixagevimab/ cilgavimab to placebo in adult patients with early-stage COVID-19. Symptomatic patients with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) test ≤ 3 days prior to the start of the study were enrolled in the study. Symptoms had to have started ≤ 7 days prior to enrolment in the study and still be present within 24 hours prior to the start of the study. At the time of study enrolment, patients should not be hospitalised and should not require supplemental oxygen (oxygen saturation ≥ 92% for indoor air). At least 60% of the patients should be at high risk of progressing to severe COVID-19. This was defined in the study based on the risk factors of age ≥ 65 years, cancer, chronic lung disease/ asthma, obesity, hypertension, cardiovascular disease, diabetes mellitus, chronic kidney disease, weakened immune system (due to organ transplantation, blood or bone marrow transplantation, immunodeficiencies, HIV, use of corticosteroids or other immunosuppressive medicines), chronic liver disease, sickle cell anaemia and smoking. These criteria correspond to the RKI risk criteria for progressing to severe COVID-19. In addition, patients who had received at least one vaccination against SARS-CoV-2 were excluded from the study. Consequently, only patients without vaccination protection were considered in the TACKLE study.

A total of 910 patients were randomised in a 1:1 ratio. Stratification was based on the risk of progressing to severe disease (high risk vs low risk) and the time since onset of symptoms (≤ 5 vs > 5 days). Approximately 90% of the patients had a high risk of progressing to severe disease according to the criteria mentioned above.

The pharmaceutical company will present the results of a pre-specified sub-population of those patients who received the study medication according to the product information within 7 days after the onset of the first COVID-19 symptoms and who were not hospitalised at the start of the study. This includes a total of 834 patients, 413 of whom were treated with tixagevimab/ cilgavimab and 421 with placebo. The sub-population submitted by the pharmaceutical company does not fully correspond to the present issue. However, the results from the subgroup analyses available in the dossier show that the patients with a low risk of progressing to severe disease included in the sub-population submitted by the pharmaceutical company have no relevant influence on the results. In addition, patients who were hospitalised for isolation at the start of the study (< 8% of the study population) are not included in the sub-population submitted by the pharmaceutical company. Despite the existing limitations, the relevance of the sub-population submitted by the pharmaceutical company is not questioned.

The primary endpoint of the study is the combined endpoint of severe COVID-19 or death of any kind until day 29. Patient-relevant secondary endpoints were endpoints on morbidity and adverse events.

Implementation of the appropriate comparator therapy

In particular, anti-inflammatory and analgesic active ingredients were administered as concomitant therapies for the treatment of COVID-19 in the TACKLE study. These were administered more or less equally often in both study arms. Other concomitant therapies frequently used in the study reflect the underlying diseases of the enrolled patients with risk factors for severe disease progression. Despite the increasing availability and use of antivirals and monoclonal antibodies, the concomitant treatment with anti-inflammatory and analgesic agents in the TACKLE study currently represents, in the view of the G-BA, an overall sufficient implementation of the appropriate comparator therapy in the present therapeutic indication.

Transferability to the current pandemic situation in Germany

Patients with at least one vaccination against SARS-CoV-2 were excluded from the TACKLE study. In contrast, at the time of the benefit assessment, a large percentage of the population already has sufficient immunisation through adequate vaccination protection and/or past exposure to the virus. Immunisation significantly reduces the risk of progression to severe COVID-19. A high percentage of patients who had an increased risk of a severe course of the disease at the time the study was carried out can therefore no longer be classified in the group of patients with increased risk as a result of immunisation. However, patients with immunosuppressive therapy (e.g. immunosuppression after organ transplantation, chemotherapy), an immunosuppressive disease or of very old age are excluded from this, as they may not be able to build up sufficient immune protection despite immunisation, so that there is still an increased risk of a severe course of the disease, regardless of vaccination protection. In addition, this includes patients who have at least one pre-existing risk factor for disease progression to even hospitalisation or are ≥ 60 years old and have not yet been vaccinated. Overall, the patient population b) is therefore considered as a whole, regardless of the vaccination status.

Furthermore, the Omicron viral variants, in which the risk of progressing to severe COVID-19 and the observed number of hospitalisations are significantly lower, were not detected in the study participants examined.

Despite the major uncertainties described here, the transfer of the results from the not vaccinated patients enrolled in the TACKLE study to patient groups who do not achieve complete immunisation despite vaccination or who have complex risk factors despite immunocompetence and complete vaccination is possible in principle. Therefore, the present study is used to assess the additional benefit in patients who have not yet received a vaccination against SARS-CoV-2 or who have not been fully immunised against SARS-CoV-2, or who, despite immunocompetence and complete vaccination, are still at increased risk for a severe course of COVID-19 due to complex risk factors and who are infected with a viral variant against which tixagevimab/ cilgavimab has sufficient efficacy (patient population b).

<u>Extent and probability of the additional benefit</u>

<u>Mortality</u>

For the endpoint overall mortality no statistically significant difference was detected between the treatment groups.

Morbidity

Severe COVID-19

In the TACKLE study, the endpoint of severe COVID-19 is operationalised as the occurrence of at least one of the following events until day 29:

- Pneumonia (fever, cough, tachypnoea or dyspnoea and pulmonary infiltrates)
- Hypoxaemia (oxygen saturation < 90% in indoor air and/or severe dyspnoea)
- WHO clinical progression scale score for COVID-19 of 5 or higher

The events included in the endpoint are suitable to adequately represent the severe course of COVID-19, as they correspond to severe symptomatology. A WHO score of 5 or higher also means that the patients are hospitalised and require the administration of oxygen. Furthermore, the results of this operationalisation are comparable to the results of the survey of severe COVID-19 operationalised as hospitalisation for COVID-19. Therefore, only the results of this operationalisation are used for the benefit assessment and presented in the resolution.

For the endpoint of severe COVID-19, there is a statistically significant difference between the treatment groups to the advantage of tixagevimab/ cilgavimab.

Admission to an intensive care unit due to any cause

The endpoint of *admission to an intensive care unit for any cause* represents a further operationalisation of the disease progression and is used for the benefit assessment. For the endpoint of *admission to an intensive care unit for any cause*, there is no statistically significant difference between the treatment groups.

Other morbidity endpoints (severe respiratory failure; hospitalisation for any cause)

The pharmaceutical company submits evaluations on further endpoints which, from its point of view, reflect the disease progression. These are hospitalisation for any cause and the endpoint of respiratory failure. The endpoint of respiratory failure is already mapped via the endpoint of severe COVID-19 and is therefore not used for the benefit assessment; the results are presented additionally.

A WHO score of 5 or higher in the operationalisation of the endpoint of *severe COVID-19* means that patients are hospitalised and require administration of oxygen. Due to the partly overlapping operationalisation of the endpoints of *severe COVID-19 and hospitalisation for any cause*, double recording of events cannot be excluded. Nevertheless, the results on the percentage of patients with hospitalisation for any cause are used for the benefit assessment, as the total hospitalisation in the present therapeutic indication is considered patient-relevant. For hospitalisation for any cause, there is a statistically significant difference between the treatment groups to the advantage of tixagevimab/ cilgavimab.

Return to normal health

The endpoint of return to normal health was to be collected in the TACKLE study daily from day 1 up to and including day 29 using a binary assessment (yes/ no) for the period of the last 24 hours based on the patients' assessment. In the TACKLE study, the time to return to the normal health status was operationalised as the time until the day on which the normal health status was restored according to the patients' assessment.

For the endpoint of return to normal health, there is no statistically significant difference between the treatment groups.

COVID symptomatology

No suitable data are available for the endpoint of COVID-19 symptomatology. The analyses submitted by the pharmaceutical company cannot be meaningfully interpreted, as no statements can be made about the distress of the patients. This concerns both the consideration of individual symptoms and the responder analysis presented. Thus, only events in which already existing symptoms have worsened are considered in the responder analysis, but not improved or newly emerged symptoms.

Quality of life

Endpoints on health-related quality of life were not collected in the included study.

Side effects

SAEs, severe AEs and discontinuations due to AEs

For the endpoint of SAEs, there is no statistically significant difference between the treatment groups. No suitable data are available for the endpoint of severe AEs, as the assessment of the severity of AEs was not based on an established classification, but on categories defined by the pharmaceutical company. No events occurred in the endpoint of discontinuation due to AEs.

Hypersensitivity reactions and reactions at the injection site

Hypersensitivity reactions and reactions at the injection site were recorded in the TACKLE study, but not using pre-specified criteria. Furthermore, it is unclear which events were included in the evaluations submitted by the pharmaceutical company. Therefore, no appropriate data are available for the endpoint of hypersensitivity reactions and reactions at the injection site.

Overall assessment/ conclusion

For the benefit assessment, the double-blind, randomised controlled trial TACKLE is available, which compared tixagevimab/ cilgavimab versus placebo in non-hospitalised patients in the early phase of COVID-19 disease who did not require supplemental oxygen therapy.

In the mortality category, for the endpoint of overall mortality, there was no statistically significant difference between the treatment groups.

The morbidity endpoints of *severe COVID-19*, *hospitalisation for any cause*, *admission to an intensive care unit for any cause* and *return to normal health* are used for the benefit assessment. For the endpoints of *severe COVID-19* and *hospitalisation for any cause*, there are statistically significant differences to the advantage of tixagevimab/ cilgavimab. However, due to the partially overlapping operationalisation of the two endpoints, double recording of events cannot be excluded. The other endpoints of *admission to an intensive care unit for any cause* and *return to normal health* show no statistically significant differences between the treatment groups.

No endpoints were collected in the category of health-related quality of life. For the endpoints in the side effects category, there are neither advantages nor disadvantages of tixagevimab/ cilgavimab.

In summary, there are positive effects in the morbidity category, which are not countered by any negative effects.

In the overall assessment of the results based on the positive effects in the endpoints of *severe COVID-19* and *hospitalisation for any cause*, a minor additional benefit compared to therapy according to doctor's instructions is derived for adults with COVID-19 disease for the treatment of infections with a viral variant for which tixagevimab/ cilgavimab has sufficient neutralisation activity.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on the randomised, double-blind TACKLE study.

The risk of bias is rated as low for the study presented at the study level. The endpoint-specific risk of bias is rated low for the results on all endpoints except the endpoint of serious adverse events (SAEs).

Regardless of this, uncertainties remain regarding the transferability of the study results to the German healthcare context. The transfer of the results from the unvaccinated patients enrolled in the TACKLE study to patient groups who do not achieve complete immunisation despite vaccination or who have complex risk factors despite immunocompetence and complete vaccination is possible in principle. However, it remains unclear whether the observed effects of the unvaccinated patients can be transferred to these patient groups without restriction. The reliability of the study data for the present research question is therefore reduced overall. Overall, therefore, relevant uncertainties remain with regard to transferability to the German healthcare context, which in the overall assessment of the reliability of data justify the derivation of a hint for an additional benefit.

c) Adolescents aged 12 to < 18 years weighing at least 40 kg with COVID-19 who do not require supplemental oxygen therapy and are at increased risk of progressing to severe COVID-19

For the treatment of adolescent patients with COVID-19, who do not require supplemental oxygen therapy and are at an increased risk of progressing to severe COVID-19, the additional benefit is not proven.

Justification:

No data are available for adolescents 12 to < 18 years old weighing at least 40 kg who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19 (see study description for patient population b). It also does not provide sufficient justification for transferability of the results to adolescents aged 12 and older. Since no data is available, no differentiated statement can be made on the effect on the different viral variants. For this age group, an additional benefit of tixagevimab/ cilgavimab is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Evusheld with the active ingredient tixagevimab/ cilgavimab. Tixagevimab/ cilgavimab is approved for the treatment of COVID-19 in adults and adolescents 12 years and older, weighing at least 40 kg, who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19.

In the therapeutic indication under consideration, three patient groups were distinguished depending on virus variants and patient age. The appropriate comparator therapy was determined by G-BA to be a therapy according to doctor's instructions.

The pharmaceutical company submits the TACKLE study for the benefit assessment.

Treatment with tixagevimab/ cilgavimab is currently not considered as a rule since tixagevimab/ cilgavimab shows significantly reduced or no efficacy against the currently dominant viral variants of SARS-CoV-2 based on in vitro neutralisation tests.

About patient group a):

In the TACKLE study, only patients infected with viral variants for which there was sufficient neutralisation activity were examined. For adults infected with a viral variant of SARS-CoV-2 for which there is insufficient neutralisation activity of tixagevimab/ cilgavimab, no statement on the additional benefit of treating COVID-19 with tixagevimab/ cilgavimab is possible. For this patient population, an additional benefit of tixagevimab/ cilgavimab compared to the appropriate comparator therapy is not proven.

About patient group b):

In the mortality category, for the endpoint of overall mortality, there was no statistically significant difference between the treatment groups. The morbidity endpoints of *severe COVID-19* and *hospitalisation for any cause* show statistically significant differences to the advantage of tixagevimab/ cilgavimab. However, due to the partially overlapping operationalisation of the two endpoints, double recording of events cannot be excluded. The other endpoints of *admission to an intensive care unit for any cause* and *return to normal health* show no statistically significant differences between the treatment groups.

No endpoints were collected in the category of health-related quality of life. For the endpoints in the side effects category, there are neither advantages nor disadvantages of tixagevimab/ cilgavimab.

Due to the limitations regarding the transferability of the study results to the current German healthcare context, the reliability of the study data for the present research question is reduced overall.

In the overall assessment, a hint for a minor additional benefit of tixagevimab/ cilgavimab over a therapy according to doctor’s instructions is derived for adults infected with a viral variant for which tixagevimab/ cilgavimab has sufficient efficacy.

About patient group c):

No data is available in the TACKLE study for adolescents 12 to < 18 years old weighing at least 40 kg who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19. For this age group, an additional benefit of tixagevimab/ cilgavimab is therefore not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The division of the patient populations results from an infection of the patients with a viral variant against which tixagevimab/ cilgavimab has sufficient or significantly limited efficacy based on in vitro neutralisation tests. According to current information from the RKI[3], 100% of infections in Germany are currently attributable to the Omicron variants.

The viral variants for which tixagevimab/ cilgavimab was able to show sufficient efficacy are no longer circulating in Germany at this time.

Accordingly, there are currently no patients in Germany who are infected with a viral variant against which tixagevimab/ cilgavimab has a significantly limited efficacy or none.

The decision to use tixagevimab/ cilgavimab for the treatment of COVID-19 shall take into account the findings on the characteristics of the circulating SARS CoV-2 viruses, including regional or geographical differences, and the available information on their sensitivity patterns to tixagevimab/ cilgavimab.

Treatment with tixagevimab/ cilgavimab is currently not considered as a rule since the medicinal product to be assessed against the currently dominant viral variants of SARS-CoV-2 shows a significantly reduced efficacy or none based on in vitro neutralisation tests. Only in patients with relevant immunosuppression and/or prolonged viral excretion can the use of tixagevimab/ cilgavimab as combination therapy with antivirals be considered in specific cases, provided that tixagevimab/ cilgavimab is not assessed as ineffective against the predominant or proven viral variant.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Evusheld (active ingredient: tixagevimab/ cilgavimab) at the following publicly accessible link (last access: 10 February 2023):

https://www.ema.europa.eu/en/documents/product-information/evusheld-epar-product-information_en.pdf

For tixagevimab/ cilgavimab, a considerably reduced (BA.1, BA.4, BA.5) or no (BQ.1/BQ.1.1, BA.4.6, BF.7.XBB) efficacy against the Omicron[3] viral variants circulating in Germany at the time of drafting the resolution was demonstrated by *in vitro* neutralisation tests. These variants were not investigated in the label-enabling TACKLE study. The study participants examined were infected with the viral variants alpha, B.1.1.519, gamma and delta.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2023).

[3] RKI weekly situation report on the coronavirus disease-2019 (COVID-19) (02.03.2023)

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tixagevimab/ cilgavimab	2 x daily	1	1	1
Therapy according to doctor's instructions	Different from patient to patient			
Appropriate comparator therapy				
Therapy according to doctor's instructions	Different from patient to patient			

Consumption:

The (daily) doses recommended in the product information were used as the calculation basis.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tixagevimab/ cilgavimab	150 mg / 150 mg	300 mg / 300 mg	2 x 150 mg / 150 mg	1	2 x 150 mg / 150 mg
Therapy according to doctor's instructions	Different from patient to patient				
Appropriate comparator therapy					
Therapy according to doctor's instructions	Different from patient to patient				

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Tixagevimab/ cilgavimab	1 SFI	€ 2,496.76	€ 2.00	€ 238.80	€ 2,255.96
Therapy according to doctor's instructions	Different from patient to patient				
Appropriate comparator therapy					
Therapy according to doctor's instructions	Different from patient to patient				
Abbreviation: SFI = solution for injection					

LAUER-TAXE® last revised: 15 March 2023

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

For the administration of tixagevimab/ cilgavimab, a uniform flat-rate remuneration for services provided by SHI-accredited physicians is granted in accordance with the Monoclonal Antibody Regulation (MAKV; valid till 7 April 2023). The reimbursement for the administration of tixagevimab/ cilgavimab in a patient infected with SARS-CoV-2 is € 360.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
Medicinal product to be assessed				
Tixagevimab/ cilgavimab	Therapy with monoclonal antibodies in patients infected with the coronavirus SARS-CoV-2	1	€ 360.00	€ 360.00

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Tixagevimab/ cilgavimab

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 10 August 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 October 2022, the pharmaceutical company submitted a dossier for the benefit assessment of tixagevimab/ cilgavimab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 3 VerfO.

By letter dated 17 October 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient tixagevimab/ cilgavimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 January 2023, and the written statement procedure was initiated with publication on the G-BA website on 16 January 2023. The deadline for submitting written statements was 6 February 2023.

The oral hearing was held on 20 February 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 5 April 2023, and the proposed resolution was approved.

At its session on 20 April 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 August 2021	Determination of the appropriate comparator therapy
Working group Section 35a	15 February 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	20 February 2023	Conduct of the oral hearing
Working group Section 35a	1 March 2023 15 March 2023 22 March 2023 5 April 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	12 April 2023	Concluding discussion of the draft resolution
Plenum	20 April 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 April 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken