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, pre-exposure prophylaxis, ≥ 12 years)

of 2 November 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 on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The medicinal product Evusheld with the combination of active ingredients tixagevimab/ cilgavimab was approved on 25 March 2022 in the indication COVID-19, pre-exposure prophylaxis, ≥ 12 years of age. Evusheld was listed on 15.06.2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. The medicinal product Evusheld was reimbursable in the indication COVID-19, pre-exposure prophylaxis, ≥ 12 years at that time in accordance with Section 1a of the CoV-2 Medicinal Products Supply Ordinance under the conditions specified therein. A benefit assessment was not initially carried out because reimbursability was limited until 25 November 2022 and it was therefore unclear whether reimbursability existed at the time of the resolution on the benefit assessment.

With the entry into force of the Ordinance on the Entitlement to Vaccination and Pre-exposure Prophylaxis against COVID-19 (COVID-19 Prevention Ordinance) on 8 April 2023, long-term reimbursement of prescription-only medicinal products for pre-exposure prophylaxis against coronavirus disease 2019 (COVID-19) was established for the first time.

The relevant date for the start of the benefit assessment procedure was 8 May 2023 for the combination of active ingredients tixagevimab/ cilgavimab in the therapeutic indication "for pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg" in analogous application of the provision in Chapter 5 Section 8, paragraph 1, No. 3 VerfO.

The pharmaceutical company submitted a dossier for the combination of active ingredients tixagevimab/ cilgavimab for the therapeutic indication COVID-19, pre-exposure prophylaxis, ≥ 12 years within the deadline of 8 May 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 August 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

Therapeutic indication of the resolution (resolution of 2 November 2023):

EVUSHELD is indicated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg, who are entitled to a supply of this medicinal product in accordance with Section 2 paragraph 1 of the COVID-19 Prevention Ordinance.

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults and adolescents aged 12 years and older weighing at least 40 kg for pre-exposure prophylaxis of COVID-19

Appropriate comparator therapy:

- Monitoring wait-and-see approach

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. The combination of active ingredients casirivimab/ imdevimab is approved for pre-exposure prophylaxis of COVID-19.[2]

on 2. In the therapeutic indication of pre-exposure prophylaxis of COVID-19, no non-medicinal treatments that are covered by statutory health insurance are indicated.

on 3. There are no G-BA resolutions in the therapeutic indication of pre-exposure prophylaxis of COVID-19.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

[2] Reimbursability of prescription-only medicinal products for pre-exposure prophylaxis of COVID-19 in accordance with Section 2 COVID-19 Prevention Ordinance for a limited group of insured persons (see also 2.1.3).

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 indication according to Section 35a, paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

Pre-exposure prophylaxis of COVID-19 for subjects 12 years and older weighing at least 40 kg is carried out in Germany as a rule in accordance with the Standing Committee on Vaccination of the Robert Koch Institute (STIKO) with approved vaccines (active immunisation) and by observing generally recognised hygiene measures (e.g. keeping a distance, observing hygiene measures, wearing filtering face-piece respirators (FFR)).

Approved medicinal products for pre-exposure prophylaxis of COVID-19[2] are the combinations of active ingredients casirivimab/ imdevimab and tixagevimab/ cilgavimab. Casirivimab/ imdevimab does not show sufficient neutralisation activity against the omicron viral variants primarily circulating at the time of the resolution. Casirivimab/ imdevimab for pre-exposure prophylaxis of COVID-19 is presently not included in the current recommendations and guidelines and is also not on the market in Germany. This is currently not considered as an appropriate comparator therapy.

In the therapeutic indication of pre-exposure prophylaxis of COVID-19, no non-medicinal treatments that are covered by statutory health insurance are indicated. There are no G-BA resolutions in the therapeutic indication of pre-exposure prophylaxis of COVID-19. Currently, measures to prevent COVID-19 disease are limited to reducing the likelihood of exposure through generally accepted hygiene measures (e.g. keeping a distance, observing hygiene measures, wearing filtering face-piece respirators), as well as the use of the approved SARS-CoV-2 vaccines.

In the overall assessment of the evidence and clinical practice, the G-BA considers "monitoring wait-and-see approach" to be an appropriate comparator therapy for tixagevimab/ cilgavimab at the current time.

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

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.

<u>About the patient populations</u>

Tixagevimab/ cilgavimab has different neutralisation activity against the different SARS-CoV-2 variants and their sublines. In vitro studies show reduced or absent neutralisation activity for tixagevimab/ cilgavimab against other Omicron strains compared to the wild type. The decision to use tixagevimab/ cilgavimab for the pre-exposure prophylaxis 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.

No data are available on the pre-exposure prophylaxis of COVID-19 in adolescents 12 years and older weighing at least 40 kg. It also does not provide sufficient justification for transferability of the results to adolescents 12 years and older.

Nevertheless, a breakdown of the patient populations is not included in the present resolution as no suitable data were submitted for the benefit assessment.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit has not been proven for pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years and older weighing at least 40 kg.

Justification:

For the benefit assessment, the pharmaceutical company presents the PROVENT study.

The PROVENT study (observation period November 2020 - February 2023) is a double-blind RCT comparing COVID-19 pre-exposure prophylaxis with tixagevimab/ cilgavimab versus placebo in unvaccinated adults at the start of study who are at increased risk of inadequate vaccine response or SARS-CoV-2 infection according to predefined inclusion criteria.

A total of 5,254 subjects were randomised to the treatment arms in a 2:1 ratio.

For the benefit assessment in accordance with Section 35a SGB V, only the patient population for which reimbursability is given at the time of the resolution is taken into account.

In accordance with Section 2 COVID-19 Prevention Ordinance, insured persons are only entitled to the provision of prescription-only medicinal products for pre-exposure prophylaxis of COVID-19 at the expense of the statutory health insurance if

1. for medical reasons, no or insufficient immune protection against COVID-19 can be achieved through vaccination, or
2. they cannot be vaccinated against the SARS-CoV-2 coronavirus due to a contraindication and they have risk factors for a severe course of COVID-19.

Medical reasons within the meaning of sentence 1 number 1 may include, in particular, congenital or acquired immunodeficiencies, underlying diseases or a significant impairment of the immune response due to immunosuppressive therapy.

For the benefit assessment, the pharmaceutical company therefore submits the results of a sub-population for which, from the pharmaceutical company's point of view, there is an entitlement to the provision of prescription-only medicinal products for preventive use to protect against COVID-19 at the expense of the SHI according to the criteria of the Section 2 COVID-19 Prevention Ordinance. It derives the sub-population on the basis of the following criteria:

1. Presence of an immunosuppressive disease at baseline
2. Treatment with immunosuppressants at baseline
3. Subjects with an impaired immune system (due to organ or bone marrow transplants, primary immunodeficiency, HIV, therapy with corticosteroids or other immunosuppressive active ingredients) who are also at increased risk of an inadequate vaccination response
4. Contraindication to SARS-CoV-2 vaccines in the presence of at least one risk factor for a severe course of COVID-19

Taking into account the above criteria, the sub-population submitted by the pharmaceutical company for the present research question comprises 519 (9.9%) of the 5,254 study

participants in the PROVENT study (tixagevimab/ cilgavimab arm N = 346; placebo arm N = 173).

The derivation of the sub-population presented by the pharmaceutical company is subject to considerable uncertainty.

In order to determine the target population for which there is an entitlement to the provision of prescription-only medicinal products for pre-exposure prophylaxis of COVID-19 at the expense of the SHI in accordance with Section 2 COVID-19 Prevention Ordinance, medical criteria must be used in addition to the text of the ordinance. In particular, it must be defined for which patients no or insufficient immune protection against COVID-19 can be achieved through vaccination for medical reasons. For this purpose, the STIKO has published an "Orienting classification of the degree of immunodeficiency and serological control after COVID-19 vaccination depending on the expected vaccination response" for medical practice, in which common diseases or frequently used therapeutics with varying degrees of immunosuppressive effect are classified according to their expected restriction of the vaccination response.[3] These criteria appear suitable for deriving the target population and are used to check the eligibility of the sub-population submitted by the pharmaceutical company.

The second basis for the claim is based on the existence of contraindications to SARS-CoV-2 vaccines. Overall, these occur rarely. If there is a contraindication to a vaccine, alternative preparations are usually also available. It can be assumed that it is very rare that a person cannot be vaccinated with the currently approved vaccines.[4]

Criterion 1: immunosuppressive disease at the start of study

The pharmaceutical company states that this criterion was operationalised via the system organ class (SOC) "Immune system disorders" according to MedDRA, with the exception of the high level group term "Allergic diseases". However, the pharmaceutical company does not provide any information on the specific underlying diseases and the respective severity of the disease. Taken together, it cannot be justified that a relevant restriction of the vaccination response can be assumed for the total of 25 study participants enrolled via this criterion, 6 of whom were included exclusively via this criterion.

Criterion 2: Treatment with immunosuppressants at the start of study

According to the information provided by the pharmaceutical company, this criterion was used to include patients who, as concomitant medication at the start of study, were receiving a medicinal product belonging to the therapeutic subgroups "antineoplastic agents" (ATC2 = L01) or "immunosuppressants" (ATC2 = L04) of the Anatomical Therapeutic Chemical (ATC) classification. No information is available on the immunosuppressive active ingredients used or their dosages and on the underlying diseases. However, according to the STIKO, the restriction of the immune response depends on the severity of the disease and the dosage of the immunosuppressive active ingredients used, so that the use of immunosuppressants is

3 Robert Koch Institute. Epidemiological Bulletin: STIKO: 25. Update of the COVID-19 vaccination recommendation; last revised: 23.02.2023 [online]. 2023 [last access: 17.10.2023]. S.15 URL: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2023/Ausgaben/08_23.pdf?__blob=publicationFile.

4 Robert Koch Institute. Epidemiological Bulletin: STIKO: 21. Update of the COVID-19 vaccination recommendation; last revised: 18.08.2022 [online]. 2022 [last access: 17.10.2023]. S.42 URL: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2022/33/Tabelle.html

not always associated with a relevant restriction of the vaccination response. A total of 163 study participants were enrolled in the sub-population presented by the pharmaceutical company via this criterion, 9 of whom were included exclusively via this criterion.

Criterion 3: Impairment of the immune system (due to organ or bone marrow transplants, primary immunodeficiency, human immunodeficiency virus (HIV), therapy with corticosteroids or other immunosuppressive active ingredients) with a simultaneous increased risk of an inadequate vaccination response

The majority of the sub-population submitted by the pharmaceutical company was included via the 3rd criterion "impairment of the immune system" (a total of 495 study participants, 324 of whom were exclusively enrolled via this criterion).

Patients were included in the sub-population via criterion 3 in accordance with the information provided by the pharmaceutical company if the presence of "impairment of the immune system due to solid organ transplantation, blood or bone marrow transplantation, immunodeficiency, HIV infection, use of corticosteroids or other immunosuppressive medicines" was documented by the principal investigator in the Case Report Form (CRF).

The information submitted in the written statement procedure shows that 225 study participants (43% of the submitted sub-population) were infected with HIV. It is unclear for how many study participants this was the only reason for inclusion in the sub-population. According to the STIKO guidelines, the presence of an HIV infection is not generally considered to be an impairment of the immune system that is associated with a relevant restriction of the vaccination response. A relevant restriction of the vaccination response can only be assumed in HIV patients with ≤ 200 CD4+ cells and/or a detectable viral load. Information on how many patients this applied to is not available for the PROVENT study.

In the CRF, "impairment of the immune system" is also defined as therapy with corticosteroids or other immunosuppressive active ingredients. In its statement, the pharmaceutical company submitted a list of the immunosuppressive active ingredients used as part of the concomitant medication, which, however, does not include any information on the number of study participants concerned or the form or dosage used. The degree of existing immunosuppression and the expected vaccination response cannot be derived from this, nor can the number of patients selected using this criterion.

Overall, with the present operationalisation of the criterion "impairment of the immune system", it remains unclear to what extent the immunodeficiency documented by the principal investigator is also associated with an expected relevant restriction of the vaccination response.

Criterion 4: Contraindication to SARS-CoV-2 vaccines in the presence of at least one risk factor for a severe course of COVID-19

This criterion was used to enrol patients for whom the item "intolerance to vaccine" was determined in the CRF by a principal investigator and for whom there was also at least one risk factor for a severe course of COVID-19. The operationalisation is comprehensible, but only 10 study participants were included in the sub-population using this criterion.

In summary, the sub-population of the PROVENT study presented by the pharmaceutical company is unsuitable for deriving an additional benefit of tixagevimab/ cilgavimab compared with the appropriate comparator therapy, as the information presented by the pharmaceutical company on the characteristics of the study participants included in the sub-

population is insufficient to justify an expected relevant restriction of the vaccination response and thus the relevance of the presented sub-population for the benefit assessment.

Conclusion:

Overall, no conclusions on the additional benefit of tixagevimab/ cilgavimab compared with the appropriate comparator therapy in the sub-population relevant for the benefit assessment can be drawn on the basis of the study results presented, as it remains unclear whether the study sub-population used by the pharmaceutical company corresponds to the sub-population relevant for the benefit assessment. An additional benefit is not proven.

2.1.4 Summary of the assessment

This assessment concerns the benefit assessment of the combination of active ingredients tixagevimab/ cilgavimab in the therapeutic indication: for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years and older weighing at least 40 kg.
For the benefit assessment in accordance with Section 35a SGB V, only the patient population for which reimbursability is given at the time of the resolution is taken into account.

In accordance with Section 2 COVID-19 Prevention Ordinance, there is an entitlement to the provision of prescription-only medicinal products for pre-exposure prophylaxis of COVID-19 at the expense of the statutory health insurance if no or insufficient immune protection against COVID-19 can be achieved by vaccination for medical reasons or vaccinations cannot be carried out due to a contraindication and there are risk factors for a severe course of COVID-19.

The G-BA determined the "monitoring wait-and-see approach" as the appropriate comparator therapy. For the benefit assessment, the pharmaceutical company presented the double-blind PROVENT RCT comparing COVID-19 pre-exposure prophylaxis with tixagevimab/ cilgavimab versus placebo.

For the benefit assessment, the pharmaceutical company submits the results of a sub-population for which, according to the criteria of Section 2 COVID-19 Prevention Ordinance, there is an entitlement to the provision of prescription-only medicinal products for preventive use to protect against COVID-19 at the expense of the SHI.

This sub-population of the PROVENT study submitted by the pharmaceutical company is unsuitable for deriving an additional benefit of tixagevimab/ cilgavimab compared with the appropriate comparator therapy, as the information submitted by the pharmaceutical company on the characteristics of the study participants included in the sub-population is insufficient to justify an expected relevant restriction of the vaccination response and thus the relevance of the submitted sub-population for the benefit assessment.

Overall, no conclusions on the additional benefit of tixagevimab/ cilgavimab compared with the appropriate comparator therapy in the sub-population relevant for the benefit assessment can be drawn on the basis of the study results presented, as it remains unclear whether the study sub-population used by the pharmaceutical company corresponds to the sub-population relevant for the benefit assessment. An additional benefit is 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 distribution of the patient populations is based on the circulation of predominantly viral variants against which tixagevimab/ cilgavimab has significantly reduced or insufficient neutralisation activity. According to current information from the ECDC, 100% of infections in Europe are currently attributable to the Omicron variants.[5]

The viral variants for which tixagevimab/ cilgavimab was able to show sufficient neutralisation activity 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 neutralisation activity or none.

The decision to use tixagevimab/ cilgavimab for the pre-exposure prophylaxis 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.

Pre-exposure prophylaxis 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 neutralisation activity or none based on in vitro neutralisation tests.

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: 28 July 2023):

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

For tixagevimab/ cilgavimab, a significantly reduced (BA.1, BA.4, BA.5) or no (BQ.1/BQ.1.1, BA.4.6, BF.7. XBB) efficacy against the omicron viral variants circulating in Germany at the time of drafting the resolution was demonstrated by in vitro neutralisation tests.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 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

[5] Country overview report: week 39 2023; https://covid19-country-overviews.ecdc.europa.eu/variants_of_concern.html

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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Adults and adolescents aged 12 years and older weighing at least 40 kg for pre-exposure prophylaxis of COVID-19

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	Single dose	1	1	1
Appropriate comparator therapy				
Monitoring wait-and-see approach	Incalculable			

Consumption:

The dose recommended in the product information was 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	150 mg/ 150 mg	1 x 150 mg/ 1 x 150 mg	1	1 x 150 mg/ 1 x 150 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Incalculable				

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 150 mg/ 150 mg	1 SFI	€ 2,496.80	€ 2.00	€ 238.80	€ 2,256.00
Appropriate comparator therapy					
Monitoring wait-and-see approach	Incalculable				
Abbreviations: SFI = solution for injection					

LAUER-TAXE® last revised: 15 October 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.

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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication)

and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the

assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the

combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults and adolescents aged 12 years and older weighing at least 40 kg for pre-exposure prophylaxis of COVID-19

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for tixagevimab/ cilgavimab (EVUSHELD); EVUSHELD 150 mg + 150 mg solution for injection; last revised: August 2023

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 6 September 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 8 May 2023, 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 10 May 2023 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 combination of active ingredients tixagevimab/ cilgavimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 August 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 August 2023. The deadline for submitting statements was 5 September 2023.

The oral hearing was held on 25 September 2023.

By letter dated 26 September 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 13 October 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 24 October 2023, and the proposed resolution was approved.

At its session on 2 November 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 September 2022	Determination of the appropriate comparator therapy
Working group Section 35a	19 September 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 September 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 October 2023 17 October 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure

Subcommittee Medicinal products	24 October 2023	Concluding discussion of the draft resolution
Plenum	2 November 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 November 2023

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

Prof. Hecken