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
Casirivimab/ Imdevimab (post-exposure prophylaxis of COVID-19 infection, ≥ 12 years)

of 6 October 2022

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## 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 forms part of the Pharmaceuticals Directive.

The subject of the present benefit assessment is the therapeutic indication of post-exposure prophylaxis. Pure pre-exposure prophylaxis is not reimbursable without proven or known risk contact. As primary prophylaxis, this is only reimbursable to the extent that there is a separate basis for claims in SGB V (cf. e.g., Section 20j SGB V).

## 2. Key points of the resolution

On 18 March 2021, the G-BA decided on an exemption to temporarily suspend the obligation to submit the dossier in benefit assessment procedures of medicinal products for the treatment of COVID-19, which were in a so-called "rolling review" procedure of the European Medicines Agency (EMA) during the determination of an epidemic situation of national importance according to Section 5 of the Infection Protection Act (IPA). The pharmaceutical company has demonstrated for the active ingredient casirivimab/ imdevimab that the suspension requirements according to the above-mentioned resolution are met. The

obligation to submit the dossier for the active ingredient casirivimab/ imdevimab in accordance with Chapter 5, Section 11 VerfO at the time specified in Chapter 5, Section 8, paragraph 1, sentence 1 VerfO has been temporarily suspended. In a letter dated 27 April 2021, the G-BA requested the pharmaceutical company to submit a complete dossier in accordance with Chapter 5, Section 11 VerfO after the expiry of the suspension period. The temporary suspension of the obligation to transmit the file pursuant to Chapter 5, Section 11 VerfO shall not affect the legal effects linked to the relevant points in time pursuant to Chapter 5, Section 8, paragraph 1, sentence 1, nos. 1 and 2 VerfO.

In a letter dated 9 November 2021, the G-BA requested the pharmaceutical company to submit a complete dossier in accordance with Chapter 5, Section 11 VerfO after the expiry of the suspension period - in this case 5 months post-authorisation. The pharmaceutical company submitted the final dossier to the G-BA on 14 April 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 July 2022, 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 casirivimab/ imdevimab 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 casirivimab/ imdevimab.

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 Casirivimab/ Imdevimab (Ronapreve) according to the product information

Ronapreve is indicated for prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

**Therapeutic indication of the resolution (resolution of 6 October 2022):**

Post-exposure prophylaxis of COVID-19 in adults and adolescents 12 years and older weighing at least 40 kg.[2]

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.
[2] The subject of the present benefit assessment is the therapeutic indication of post-exposure prophylaxis. Pure pre-exposure prophylaxis is not reimbursable without proven or known risk contact according to SGB V. As primary prophylaxis, this is only reimbursable to the extent that there is a separate basis for claims in SGB V (cf. e.g., Section 20j SGB V). Currently, there is only a time-limited reimbursability through the "Third Regulation for the Amendment to the SARS-CoV-2 Pharmaceutical Price Ordinance".

a) Adults and adolescents weighing at least 40 kg for post-exposure prophylaxis of COVID-19 following exposure to viral variants for which casirivimab/ imdevimab has insufficient efficacy.

**Appropriate comparator therapy for post-exposure prophylaxis:**

Monitoring wait-and-see approach

b) Adults and adolescents weighing at least 40 kg and without complete immunisation for post-exposure prophylaxis of COVID-19 after exposure to viral variants for which casirivimab/ imdevimab has sufficient efficacy.

**Appropriate comparator therapy for post-exposure prophylaxis:**

Monitoring wait-and-see approach

c) Adults and adolescents weighing at least 40 kg and with complete immunisation for post-exposure prophylaxis of COVID-19 after exposure to viral variants for which casirivimab/ imdevimab has sufficient efficacy.

**Appropriate comparator therapy for post-exposure prophylaxis:**

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. No medicinal products have yet been approved for this therapeutic indication.

on 2. Basically, the generally accepted hygiene measures (such as keeping a distance, observing hygiene measures, wearing mouth-nose coverings) are non-medicinal measures to reduce the risk of infection.

on 3. In the mentioned therapeutic indication, there are no resolutions approved by the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V or of non-medicinal treatments.

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.

Currently, measures to prevent COVID-19 disease are limited to reducing the likelihood of exposure through generally accepted hygiene measures, as well as the use of the approved SARS-CoV-2 vaccines. Apart from a possible quarantine order, which is primarily used to reduce further risk contacts and not for individual treatment, there are no other recommendations for adults and adolescents for the prophylaxis of COVID-19. In this regard, neither approved pharmaceutical options for post-exposure prophylaxis of COVID-19 disease nor non-medicinal interventions currently exist. In the overall assessment of the evidence and clinical practice, the G-BA therefore considers monitoring wait-and-see approach to be an appropriate comparator therapy at the current time.

In distinction, the situation from the first appearance of symptoms following exposure to SARS-CoV-2 viruses and the presence of a positive SARS-CoV-2 PCR test is considered an outbreak of COVID-19. This would no longer be covered by the objective of prophylaxis, but would entail the need for active treatment according to the generally recognised state of medical knowledge in the sense of treatment of COVID-19. This constellation is also not covered by the therapeutic indication for post-exposure prophylaxis to be assessed here.

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

### 2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of casirivimab/ imdevimab is assessed as follows:

a) <u>Adults and adolescents weighing at least 40 kg for post-exposure prophylaxis of COVID-19 following exposure to viral variants for which casirivimab/ imdevimab has insufficient efficacy.</u>

An additional benefit is not proven.

Justification:

For adults and adolescents weighing at least 40 kg after exposure to viral variants for which casirivimab/ imdevimab has insufficient efficacy based on *in vitro* neutralisation tests, no conclusions on the additional benefit of post-exposure prophylaxis of COVID-19 with casirivimab/ imdevimab are possible. For this patient population, an additional benefit of casirivimab/ imdevimab for post-exposure prophylaxis compared to the appropriate comparator therapy is therefore not proven.

b) Adults and adolescents weighing at least 40 kg and without complete immunisation for post-exposure prophylaxis of COVID-19 after exposure to viral variants for which casirivimab/ imdevimab has sufficient efficacy.

   For adults and adolescents without complete immunisation after exposure to viral variants for which casirivimab/ imdevimab has sufficient efficacy, there is a hint for a minor additional benefit of casirivimab/imdevimab in the post-exposure prophylaxis of COVID-19.

Justification:

For the benefit assessment, the pharmaceutical company submits the R10933-10987-COV-2069 study (in short: COV-2069 study).
COV-2069 is a double-blind, randomised, placebo-controlled phase III study to investigate prevention with casirivimab/ imdevimab in asymptomatic adults, adolescents and children who have had contact with a person infected with SARS-CoV-2 in their own household (index case with positive SARS-CoV-2 test). Enrolment of the contact person had to take place within 96 hours after sample collection for the diagnostic test of the index case. At the time of enrolment in the study, the serostatus of the contact persons or SARS-CoV-2 antibodies was examined. However, inclusion was independent of the result of this examination, so that both subjects with negative and those with positive serostatus could be enrolled in the study. However, subjects with a positive SARS-CoV-2 RT-qPCR test or positive SARS-CoV-2 serology test at any time prior to enrolment in the study were excluded from participation in the study. Only patients without vaccination protection were included in the study; patients who had received at least one vaccination against SARS-CoV-2 were excluded from the COV-2069 study.

A total of 3,298 adults, adolescents and children were included and assigned to treatment with casirivimab/ imdevimab or placebo in a 1:1 ratio. The result of a RT-qPCR test of the central laboratory, which was additionally carried out at the start of the study, was used to assign the subjects to the cohorts of the study. Depending on the result of this RT-qPCR test and the age, the subjects were allocated to the cohorts according to the study design. For the present benefit assessment, cohorts A (SARS-CoV-2 RT-qPCR-negative at the start of the study, ≥ 12 years) and B (SARS-CoV-2 RT-qPCR-positive at the start of the , ≥ 12 years) are considered relevant for the approved therapeutic indication to be assessed here, and the evaluations for cohorts A and B are considered separately. The primary endpoint of the study was the percentage of subjects with symptomatic SARS-CoV-2 infection for cohort A and the percentage of subjects who develop symptomatic SARS-CoV-2 infection 14 days after a positive RT-qPCR test for cohort B, respectively. Patient-relevant secondary endpoints were morbidity endpoints, and AEs.

According to the casirivimab/ imdevimab product information, decisions on the application of casirivimab/ imdevimab should take into account what is known about the characteristics of the circulating SARS CoV-2 viruses, including regional or geographical differences, and the available information on their sensitivity patterns to casirivimab/ imdevimab. Based on the information in the dossier, it is unclear with which variant of the SARS-CoV-2 virus the adults and adolescents enrolled in the COV-2069 study were infected and for how many of them a genotyping of the virus was available at all. Due to the implementation period of the study in an earlier wave of the pandemic (07/2020 to 10/2021), it can be assumed that the majority of the enrolled adults and adolescents were infected with virus variants circulating before the spread of the Omicron virus variant, which was predominant at the time of the benefit assessment.

*Implementation of the appropriate comparator therapy*

The appropriate comparator therapy of monitoring wait-and-see approach as defined by the G-BA was operationalised as a follow-up strategy in the COV-2069 study. In addition, for blinding reasons, a placebo was administered in the comparator arm. Follow-up, according to the study protocol, included weekly RT-qPCR testing for SARS-CoV-2 until day 29, collection of AEs, and in the case of a positive RT-qPCR test, collection of hospitalisation, emergency department visit or emergency room visit due to COVID-19. Even though it is not clear from the information in the dossier whether the study participants were advised of preventive measures, such as wearing a mask in the household or spatial isolation, to reduce the risk of SARS-CoV-2 infection when participating in the study, it is assumed for the present benefit assessment that the implementation of preventive measures in the COV-2069 study reflects the healthcare context. In symptomatic COVID-19, therapy could be initiated according to local guidelines as assessed by the attending physician. According to the study design, there were no limitations on the medicines to be administered for symptomatic patients. Overall, the follow-up strategy in the COV-2069 study represents a sufficient implementation of the appropriate comparator therapy.

*Transferability to the current situation in Germany*

Patients with at least one vaccination against SARS-CoV-2 were excluded from the COV-2069 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.

Even if there is no regulatory restriction of COVID-19 post-exposure prophylaxis to adults and adolescents with an increased risk of a severe course of COVID-19, from a medical and epidemiological point of view there is a sensible use of post-exposure prophylaxis for these patients in particular. In the study population, the average age of the enrolled patients was 42 years and about three quarters of the patients had no risk factors for a severe course of COVID-19. It would have been of particular importance to obtain a study-based assessment of possible effects.

Overall, there are no data on patients with sufficient immunisation, and patients with an increased risk of a severe course were underrepresented in the study. Furthermore, the viral variant to which the enrolled patients were exposed is unclear. The Omicron virus variant, which was widely spread at the time of the benefit assessment and for which the risk of progressing to severe COVID-19 and the observed number of hospitalisations is significantly lower, was not yet available at the time the study was conducted.

The present study is used despite the great uncertainties described here regarding transferability to the current situation.

*Distribution of the patient population*

The patient populations of the COV-2069 study differ in such a way that a division of the total population into different patient populations is considered reasonable. Particularly with regard to immunisation and serostatus, the populations can be demarcated to such an extent that a total of three patient populations (a, b and c) must be distinguished from each other.
The Paul Ehrlich Institute (PEI) and the Division of Intensive Care, Infectious Diseases and Emergency Medicine (COVRIIN) of the Robert Koch Institute (RKI) recommend taking into account the current epidemiological situation and the neutralisation activity against the individual virus variants when choosing monoclonal antibodies for therapy or prophylaxis. Accordingly, the G-BA considers it justified to additionally form a separate patient population for adults and adolescents weighing at least 40 kg for post-exposure prophylaxis of COVID-19 after exposure to viral variants for which casirivimab/ imdevimab has insufficient efficacy based on *in vitro* neutralisation tests.

Extent and probability of additional benefit for patient population b)

Mortality

For adults and adolescents without complete immunisation, the COV-2069 study shows no statistically significant difference between the treatment groups (cohort A and B) for the endpoint of overall mortality.

Morbidity

*Symptomatic SARS-CoV-2 infection (broad definition; CDC definition; SARS-CoV-2 infection detected by RT-qPCR test)*

For symptomatic SARS-CoV-2 infection, according to the study design, a positive SARS-CoV-2 RT-qPCR test from the central laboratory had to be present within the 28-day observation period for morbidity endpoints, in conjunction with the onset of symptoms within ± 14 days of the positive test result. The symptoms could also occur outside the duration of observation.

For the endpoint of symptomatic SARS-CoV-2 infection, three different operationalisations were presented based on different criteria for the presence of symptoms: broad definition, narrow definition and *Center for Disease Control and Prevention* (CDC) definition. For this benefit assessment, symptomatic SARS-CoV-2 infection is operationalised using the broad definition. This operationalisation includes a larger number of possible COVID-19 symptoms, thus better representing the clinically variable picture of COVID-19. The broad definition also corresponds to the primary definition according to the study design. In addition, the evaluations of the CDC definition as well as SARS-CoV-2 infections detected by RT-qPCR test independent of symptoms are also presented. The latter operationalisation provides information beyond symptomatic SARS-CoV-2 infection for the present therapeutic indication of COVID-19 post-exposure prophylaxis.

The operationalisations of symptomatic SARS-CoV-2 infection chosen here cover symptoms of varying severity, whereby the mere presence of comparatively mild symptoms (e.g., runny nose or sneezing) was also counted as an event. Overall, the events included in the endpoint of symptomatic SARS-CoV-2 infection are classified as rather non-serious.

In the COV-2069 study, for the endpoint of symptomatic SARS-CoV-2 infection (broad definition), there is a statistically significant difference between the treatment groups to the advantage of casirivimab/ imdevimab in both cohorts A and B. The results between the CDC and broad definitions are comparable for the endpoint of symptomatic SARS-CoV-2 infection in each case.

In cohort A, this positive effect is also shown in the supplementary percentage of subjects with a positive SARS-CoV-2 RT-qPCR test, regardless of symptoms.

*Hospitalisation due to COVID-19*

It is not clear from the study documents and the information provided by the pharmaceutical company under which conditions a hospitalisation due to COVID-19 occurred. In addition, it remains unclear whether hospitalisation was associated with a minimum time criterion, such as a minimum duration of 24 h. Data on hospitalisation due to any cause are not available in the dossier. It is assumed that the hospitalisation was at the discretion of the attending physician.

In the present therapeutic indication, mild and moderate courses of the disease in patients usually cure in home isolation, while hospitalisation usually occurs only in case of deterioration of symptomatology due to COVID-19. Therefore, hospitalisation in the present case can be considered as approximating the clinical condition of symptom deterioration. Thus, the endpoint "hospitalisation due to COVID-19" gives conclusions about the disease-specific morbidity and is used in this case.

In cohort A of the COV-2069 study, there is no statistically significant difference between the treatment arms for the endpoint of hospitalisation due to COVID-19, while in cohort B a statistically significant difference between the treatment groups can be derived to the advantage of casirivimab/ imdevimab.

<u>Quality of life</u>

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

Side effects

*SAEs and severe AEs*

Disease-related events were included in the assessment of serious adverse events (SAEs) and severe adverse events in the COV-2069 study. It remains unclear which events were classified as disease-related and accordingly not taken into account in the evaluations. As a result, the overall rates of SAEs and severe Aes are not useful for evaluating the side effects of casirivimab/ imdevimab.

However, based on the results for frequent SAEs and frequent severe AEs, given the low percentage of subjects with events, no adverse effects of casirivimab/ imdevimab are expected to a degree that may call into question the additional benefit of casirivimab/ imdevimab.

*Discontinuation due to AEs*

In the COV-2069 study, there were no discontinuations due to AEs during the course of the study (cohorts A and B).

Overall assessment

The benefit assessment of post-exposure prophylaxis with casirivimab/ imdevimab is based on the double-blind randomised controlled trial COV-2069, which compared casirivimab/ imdevimab versus placebo.

In the endpoint category of mortality, there was no statistically significant difference in overall survival (cohorts A and B). For the mortality category, no statement on additional benefit can be derived.

For the endpoint of symptomatic SARS-CoV-2 infection (broad definition), there is a statistically significant difference to the advantage of casirivimab/ imdevimab (cohorts A and B). The extent of this advantage can only be estimated as minor, since the operationalisations chosen here also include mild symptoms (e.g., running nose or sneezing). Overall, the events included in the endpoint of symptomatic SARS-CoV-2 infection are classified as rather non-serious.

For the endpoint of hospitalisation (in cohort B), a statistically significant difference to the advantage of casirivimab/ imdevimab can also be observed.

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

Although the overall rates of SAEs and severe SAEs are not assessable for the evaluation of side effects of casirivimab/ imdevimab, based on the results for frequent SAEs and frequent severe SAEs, given the low percentage of subjects with events, no side effects of casirivimab/ imdevimab are expected to a degree that could call into question the additional benefit of casirivimab/ imdevimab. Discontinuation due to Aes did not occur in the study.

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 and primarily on the basis of the positive effects in the endpoint of hospitalisation due to COVID-19, a minor additional benefit is derived for the post-exposure prophylaxis of COVID-19 with casirivimab/ imdevimab compared to the appropriate comparator therapy for adults and adolescents without complete immunisation after exposure to viral variants for which casirivimab/ imdevimab has sufficient efficacy.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on the randomised, double-blind COV-2069 study.

The risk of bias is rated as low for the study presented at the study level. The risk of bias of the results at the endpoint level is also rated as low.

Regardless of this, uncertainties remain regarding the transferability of the study results to the current medical treatment situation in Germany.

For example, the COV-2069 study on which the assessment is based included a very broad study population. Taking into account the current high immunisation status in the German population, the use of post-exposure prophylaxis would be considered in the German healthcare context, especially for those patients who have a high risk of a severe course of the disease despite immunisation. The percentage of patients considered at risk according to the current state of medical knowledge in everyday care was only about 25 per cent in the COV-2069 study.

The operationalisations of a symptomatic SARS-CoV-2 infection chosen in the study also cover symptoms of different degrees of severity, whereby the mere presence of comparatively mild symptoms (e.g., running nose or sneezing) was already evaluated as an event.

Overall, therefore, relevant uncertainties remain with regard to transferability to the current German healthcare context, which in the overall view justify the derivation of a hint for an additional benefit considering the reliability of data.

c) Adults and adolescents weighing at least 40 kg and complete immunisation for post-exposure prophylaxis of COVID-19 after exposure to virus variants for which casirivimab/ imdevimab has sufficient efficacy

An additional benefit is not proven.

Justification:

For adults and adolescents weighing at least 40 kg and complete immunisation for post-exposure prophylaxis of COVID-19 after exposure to viral variants for which casirivimab/ imdevimab has sufficient efficacy, no conclusions on the additional benefit of post-exposure

prophylaxis of COVID-19 with casirivimab/ imdevimab are possible on the basis of the COV-2069 study, as only subjects without vaccination protection were examined in the study. For this patient population, an additional benefit of casirivimab/ imdevimab for post-exposure prophylaxis compared to the appropriate comparator therapy is therefore not proven.

### 2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Ronapreve with the active ingredient casirivimab/ imdevimab.
Casirivimab/ imdevimab is approved for the prophylaxis of COVID-19 in adults and adolescents 12 years and older weighing at least 40 kg. The therapeutic indication assessed here includes only post-exposure prophylaxis of COVID-19 within the approved therapeutic indication.

In the therapeutic indication under consideration, three patient groups were distinguished depending on virus variants and immunisation status.

<u>About patient group a)</u>

The G-BA determined the monitoring wait-and-see approach as the appropriate comparator therapy.

For adults and adolescents weighing at least 40 kg after exposure to viral variants for which casirivimab/ imdevimab does not show sufficient efficacy based on *in vitro* neutralisation tests, no data suitable for benefit assessment are available for COVID-19 post-exposure prophylaxis. For this patient population, an additional benefit of casirivimab/ imdevimab for post-exposure prophylaxis compared to the appropriate comparator therapy is not proven.

<u>About patient group b)</u>

The G-BA determined the monitoring wait-and-see approach as the appropriate comparator therapy.
For the benefit assessment, the results of the RCT COV-2069 are available for adults and adolescents without complete immunisation after exposure to viral variants for which casirivimab/ imdevimab has sufficient efficacy.

In the mortality category, no differences relevant to the benefit assessment occurred during the study. In summary, in terms of morbidity, there are statistically significant advantages in hospitalisation due to COVID-19 and symptomatic SARS-CoV-2 infection, which are considered minor in their extent. Quality of life data were not collected. In the category of side effects, the overall results do not suggest any side effects of casirivimab/ imdevimab that could, in their extent, call into question the additional benefit of casirivimab/ imdevimab in terms of morbidity. Due to the broad study population and the resulting limitations regarding the transferability of the study results to the current German healthcare context, uncertainties remain overall.

In the overall assessment, for adults and adolescents without complete immunisation after exposure to viral variants for which casirivimab/ imdevimab has sufficient efficacy, hint for a minor additional benefit compared to the appropriate comparator therapy is derived for post-exposure prophylaxis of COVID-19 with casirivimab/ imdevimab.

About patient group c)

The G-BA determined the monitoring wait-and-see approach as the appropriate comparator therapy.

For adults and adolescents weighing at least 40 kg and complete immunisation, no data suitable for benefit assessment are available for post-exposure prophylaxis of COVID-19 after exposure to viral variants for which casirivimab/ imdevimab has sufficient efficacy. For this patient population, an additional benefit of casirivimab/ imdevimab for post-exposure prophylaxis compared to the appropriate comparator therapy 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 casirivimab/ imdevimab has sufficient or insufficient 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 casirivimab/ imdevimab could show sufficient efficacy are not circulating in Germany at this time.

Accordingly, there are currently no patients in Germany who are infected with a viral variant against which casirivimab/ imdevimab has sufficient efficacy. *(Populations b and c)*

The product information of casirivimab/ imdevimab states that the decision to administer casirivimab/ imdevimab for treatment should take into account what is known about the characteristics of the circulating SARS-CoV-2 viruses, including regional or geographical differences, and the available information on their sensitivity patterns to casirivimab/ imdevimab. Since the medicinal product to be assessed does not have sufficient efficacy against the currently dominant viral variants of SARS-CoV-2 on the basis of *in vitro* neutralisation tests, no patient is currently eligible for treatment with casirivimab/ imdevimab in the *patient population a* accordingly.

## 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 Ronapreve (combination of active ingredients: casirivimab/ imdevimab) at the following publicly accessible link (last access: 2 September 2022):

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

The decision to use casirivimab/ imdevimab for treatment shall take into account the evidence on the characteristics of the circulating SARS CoV-2 viruses, including regional or geographical

[3] RKI weekly situation report on the coronavirus disease-2019 (COVID-19) (15.09.2022)

differences, and the available information on their sensitivity patterns to casirivimab/ imdevimab.

For casirivimab/ imdevimab, no sufficient efficacy could be demonstrated against variants of the Omicron virus[3] circulating alone in Germany at the time of passing the resolution using *in vitro* neutralisation tests.

### 2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information from the pharmaceutical company. As the appropriate comparator therapy is the same for all patient populations (adults and adolescents), the costs are presented together here.

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 | | | | |
| Casirivimab/ imdevimab | Single dose | 1 | 1 | 1 |
| Appropriate comparator therapy | | | | |
| Patient populations a) to c) | | | | |
| Monitoring wait-and-see approach | incalculable | | | |

Consumption:

| 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 | | | | | |
| Casirivimab/ imdevimab | 600 mg | | | | 1 x 600 mg |
| Appropriate comparator therapy | | | | | |
| Patient populations a) to c) | | | | | |
| 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 | | | | | |
| Casirivimab/ imdevimab | incalculable | | | | |
| Appropriate comparator therapy | | | | | |
| Monitoring wait-and-see approach | incalculable | | | | |

LAUER-TAXE® last revised: 15 September 2022

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 casirivimab/imdevimab, a uniform flat-rate remuneration for services provided by SHI-accredited physicians is granted in accordance with the Monoclonal Antibody Regulation (MAKV). The reimbursement for the administration of casirivimab/ imdevimab for prophylaxis in a patient not infected with SARS-CoV-2 coronavirus with an increased risk of a severe course is € 150.

| Designation of the therapy | Designation of the service | Number | Unit cost | Costs/ patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Casirivimab/ imdevimab | Prophylaxis with monoclonal antibodies in a patient not infected with SARS-CoV-2 coronavirus with an increased risk of severe progression | 1 | € 150.00 | € 150.00 |

## 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 July 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed.

On 14 April 2022, the pharmaceutical company submitted a dossier for the benefit assessment of casirivimab/ imdevimab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 19 April 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 casirivimab/ imdevimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 July 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 15 July 2022. The deadline for submitting written statements was 5 August 2022.

The oral hearing was held on 22 August 2022.

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 27 September 2022, and the proposed resolution was approved.

At its session on 06 October 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

### Chronological course of consultation

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 6 July 2021 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 5 April 2022 | Examination of the appropriate comparator therapy |

| | | |
|---|---|---|
| Working group Section 35a | 17 August 2022 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal products | 22 August 2022 | Conduct of the oral hearing |
| Working group Section 35a | 31 August 2022<br>14 September 2022<br>21 September 2022 | Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure |
| Subcommittee Medicinal products | 27 September 2022 | Concluding discussion of the draft resolution |
| Plenum | 6 October 2022 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 6 October 2022

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

Prof. Hecken