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 (COVID-19, ≥ 12 years)

of 6 October 2022

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 forms part of the Pharmaceuticals Directive.

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 treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg 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 October 2022):

see the approved therapeutic indication

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults and adolescents aged 12 years and older weighing at least 40 kg 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 casirivimab/ imdevimab has insufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

b) Adults with COVID-19 disease who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, when infected with a viral variant against which casirivimab/ imdevimab has sufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

c) 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 the case of infection with a viral variant against which casirivimab/ imdevimab has sufficient efficacy

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. Regdanvimab, remdesivir, sotrovimab and nirmatrelvir/ ritonavir are approved for the treatment of COVID-19 in patients who do not require supplemental oxygen 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.

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 (i.e., in home isolation). 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 ingredient remdesivir was assessed by the G-BA as part of the early benefit assessment. A hint for a minor additional benefit was identified for 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.

Recently, the active ingredients regdanvimab, sotrovimab and nirmatrelvir/ ritonavir have been approved for the treatment of COVID-19 patients who do not require supplementary oxygen and who are at increased risk of progressing to severe COVID-19. The active ingredient molnupiravir is not yet approved in the EU, but can be used on the basis of the general order on the purchase and use of monoclonal antibodies and on the purchase and administration of antiviral oral medicinal products against COVID-19 issued by the Federal Ministry of Health on 25 March 2022 for the treatment of COVID-19 in adults who do not require supplementary oxygen and are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time. Due to the limited experience with these active ingredients in the provision of care and due to the still pending benefit assessments, these active ingredients do not represent a component of the specific appropriate comparator therapy at this point in time.

As the disease progresses, symptoms may deteriorate and hospitalisation may be indicated due to COVID-19. This treatment setting is also no longer addressed by the present therapeutic indication for starting treatment with casirivimab/ imdevimab. 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 casirivimab/ imdevimab 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. 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 mandate.

2.1.3 Extent and probability of the additional benefit

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

a) Adults and adolescents aged 12 years and older weighing at least 40 kg with COVID-19 disease and 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 casirivimab/ imdevimab does not have sufficient efficacy

For the treatment of adult and adolescent patients with COVID-19 disease who do not require supplementary oxygen , who are at increased risk of progressing to severe COVID-19 and who are infected with a viral variant against which casirivimab/ imdevimab does not have sufficient efficacy, the additional benefit is not proven.

Justification:

Adults and adolescents infected with a SARS-CoV-2 viral variant for which there is evidence or current pandemic activity of insufficient neutralising activity of casirivimab/ imdevimab, no statement on the additional benefit of treating COVID-19 with casirivimab/ imdevimab is possible. For this patient population (patient population a), an additional benefit of casirivimab/ imdevimab compared to the appropriate comparator therapy is not proven.

b) Adults with COVID-19 disease who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, when infected with a viral variant against which casirivimab/ imdevimab has sufficient efficacy

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

Justification:

For the benefit assessment, the pharmaceutical company submits the R10933-10987-COV-2067 study (in short: COV-2067 study).

The COV-2067 study is an adaptive, placebo-controlled, double-blind, randomised phase 1/2/3 study on treatment of COVID-19 patients with casirivimab/ imdevimab. Only non-hospitalised patients in the early phase of COVID-19 disease who did not require supplemental oxygen were enrolled in the study. Depending on the study phase or cohort, both symptomatic and asymptomatic patients were enrolled in the study, as well as patients with at least one risk factor for a severe course of COVID-19 and patients without any risk factor.

The study was conducted using a common master protocol that included phases 1, 2 and 3. The data collected in phases 1 and 2 as well as data from phase 3 before protocol amendment 6 are not relevant for the benefit assessment due to the deviations from the requirements in the product information regarding the administered casirivimab/ imdevimab dose. Relevant for the benefit assessment are data on patients from phase 3 who were allocated to one of the two study arms 1200 mg casirivimab/ imdevimab or placebo under protocol amendments

6 and 7. In phase 3, casirivimab/ imdevimab was administered intravenously 1 time on day 1, followed by a 169-day follow-up period.

Patients with a positive SARS-CoV-2 antigen test or molecular diagnostic test from a sample collected > 72 hours prior to randomisation, and patients with a known history of positive SARS-CoV-2 serological test were excluded from the study from protocol amendment 6. Patients with a history of hospitalisation due to COVID-19 were also excluded from the study. In addition, patients who had received at least one vaccination against SARS-CoV-2 were excluded from the study.

Adult patients were included in cohort 1. Patients < 18 years old were included in cohort 2. Patients included in cohort 1 had to have symptoms of COVID-19 with onset ≤ 7 days before randomisation and ≥ 1 risk factor for severe disease progression. Under protocol amendments 6 and 7, a total of 4,046 patients were randomised 1:1:1 to 1200 mg casirivimab/ imdevimab (N = 1347), 2,400 mg casirivimab/ imdevimab (N = 1350) or placebo (N = 1349). The primary endpoint for cohort 1 is the combined endpoint of hospitalisation due to COVID-19 or death from any cause until day 29. Patient-relevant secondary endpoints are overall mortality and endpoints for morbidity and adverse events (AEs). Cohort 2 contains a sub-population that is fundamentally relevant for the benefit assessment. These are patients 12 to < 18 years old weighing at least 40 kg who have symptoms of COVID-19 and ≥ 1 risk factor for a severe course of the disease, but no data are available for the relevant sub-population of cohort 2 for the present benefit assessment in the dossier.

Implementation of the appropriate comparator therapy

In the COV-2067 study, the use of approved or antiviral agents against SARS-CoV-2 under investigation was not allowed according to the study design. In particular, anti-inflammatory and analgesic active ingredients were administered as concomitant therapies for the treatment of COVID-19 in the COV-2067 study. The concomitant treatment with anti-inflammatory and analgesic active ingredients in the COV-2067 study represents an overall sufficient implementation of the appropriate comparator therapy.

Transferability to the current pandemic situation in Germany

Patients with at least one vaccination against SARS-CoV-2 were excluded from the COV-2067 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, based on the information in the dossier, it is unclear with which viral variants the included patients were infected. 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.

Despite the major uncertainties described here, the transfer of the results from the unvaccinated patients enrolled in the COV-2067 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 casirivimab/ imdevimab has sufficient efficacy (patient population b).

Extent and probability of the additional benefit

Mortality

For the endpoint of overall mortality, there is a statistically significant difference between the treatment groups to the advantage of casirivimab/ imdevimab.

Morbidity

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.
For the endpoint of hospitalisation due to COVID-19, there is a statistically significant difference between the treatment groups to the advantage of casirivimab/ imdevimab.

Admission to an intensive care unit due to COVID-19
The endpoint "admission to an intensive care unit due to COVID-19" represents a further disease progression and is therefore used for the benefit assessment. For the endpoint of admission to an intensive care unit due to COVID-19, there is no statistically significant difference between the treatment groups.

Resolution of COVID-19 symptoms (SE-C19)
COVID-19 symptoms were assessed in the COV-2067 study using the SE-C19 questionnaire. The SE-C19 has been validated by the pharmaceutical company for the assessment of symptomatology in outpatients with COVID-19. The 19 symptoms enquired are fever, sore throat, cough, shortness of breath/ difficulty breathing, chills, nausea, diarrhoea, headache, red/watery eyes, aching limbs such as muscle pain, loss of taste/ smell, fatigue, appetite loss, dizziness, pressure/ tightness in the chest, chest pain, abdominal pain, runny nose and sputum/ mucus. COVID-19 symptoms were assessed by the patients daily from day 1 up to and including day 29 by means of an electronic diary for the period of the last 24 hours. The

severity grade of symptoms was rated on a 3-point scale (0: none; 1: mild/ moderate; 2: severe). The pharmaceutical company shall submit evaluations for the period until the symptoms have subsided. Resolution was defined as a score of 0 on the severity grade scale for most symptoms. Only for the symptoms headache, fatigue and cough was a value of 1 also allowed. Despite the low response rate on day 29, the evaluations presented until reduction of symptoms, collected using SE-C19, are used for the present benefit assessment.
For the endpoint of reduction of COVID-19 symptoms, assessed by SE-C19, there is a statistically significant difference between the treatment groups to the advantage of casirivimab/ imdevimab. However, there is an effect modification due to the age characteristic. For patients aged 18 to 64 years, there is no hint of an additional benefit of casirivimab/ imdevimab compared to treatment according to doctor's instructions. For patients ≥ 65 years old, however, there is a hint for an additional benefit of casirivimab/ imdevimab compared to therapy according to doctor's instructions.

Return to normal health, return to normal activities and health status (EQ-5D VAS)
The endpoints of return to normal health and return to normal activities were to be collected in the COV-2067 study using a binary assessment (yes/ no) for the period of the last 24 hours based on the patients' assessment. In addition, the patients' health status should be assessed by means of EQ-5D VAS. However, the two questionnaires and the EQ-5D VAS were only available in the study sites with a delay, so that the assessments could not be carried out for all enrolled patients. Return rates dropped sharply early on in the course of the study for all 3 instruments. Furthermore, the return rates show strong fluctuations over the course of the study.
Therefore, no usable data are available for the endpoints of return to normal health, return to normal activities and health status measured by the EQ-5D VAS.

Quality of life

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

Side effects

SAEs, severe AEs, discontinuations due to AEs and infusion-related reactions
For the endpoints of the category side effects, no usable data are available. In the assessment of SAEs and severe AEs, disease-related events were included to a large extent in the study COV-2067. Although the pharmaceutical company presents evaluations for these endpoints in the dossier that exclude disease-related events, it remains unclear which events were classified as disease-related and were therefore 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. Furthermore, discontinuations due to AEs were not systematically recorded in the study. The results on infusion-related reactions are also not usable due to uncertainties regarding the operationalisation and a prolonged infusion duration in the COV-2067 study. Overall, there are thus no usable data for assessing the side effects of casirivimab/ imdevimab. However, based on the results on frequent SAEs and severe AEs, no negative effects of casirivimab/ imdevimab are expected to a degree that could call into question the additional benefit of casirivimab/ imdevimab, given the low percentage of patients with events.

Overall assessment

For the benefit assessment, the double-blind, randomised controlled trial COV-2067 is available, which compared casirivimab/ imdevimab versus placebo in non-hospitalised patients in the early phase of COVID-19 disease who did not require supplemental oxygen.

In the mortality category, there was a statistically significant difference between the treatment groups for the endpoint of overall mortality to the advantage of casirivimab/ imdevimab.
In the morbidity category, the endpoints of hospitalisation due to COVID-19 and reduction of COVID-19 symptoms, assessed by SE-C19, showed statistically significant advantages in favour of casirivimab/ imdevimab compared to the control arm. For the other endpoint of the morbidity category, admission to an intensive care unit due to COVID-19, there is no statistically significant difference between the treatment groups. No usable data are available for the morbidity endpoints of return to normal health, return to normal activities and health status (EQ-5D VAS).
Endpoints on health-related quality of life were not assessed in the study.
For the endpoints of the category side effects, no usable data are available. However, based on the results on frequent SAEs and severe AEs, no negative effects of casirivimab/ imdevimab are expected to a degree that could call into question the additional benefit of casirivimab/ imdevimab, given the low percentage of patients with events.
In summary, there are positive effects in the categories of mortality and morbidity, which are not countered by negative effects.
In the overall assessment of the results based on the positive effects in the endpoints of overall mortality, hospitalisation due to COVID-19 and reduction of COVID-19 symptoms, a considerable additional benefit is derived for adults and adolescents for the treatment of viral variants for which casirivimab/ imdevimab has sufficient neutralising activity compared to the appropriate comparator therapy.

In summary, for adults with COVID-19 disease who do not require supplemental oxygen and who are at increased risk of severe COVID-19, there is a hint of considerable additional benefit of casirivimab/ imdevimab compared to the appropriate comparator therapy according to the doctor's instructions.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on the randomised, double-blind COV-2067 study.
The risk of bias is rated as low for the phase 3 part of the submitted study at study level. The endpoint-specific risk of bias is considered low for the results on all endpoints except the endpoint of reduction of COVID-19 symptoms.

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 included in the COV-2067 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 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 the case of infection with a viral variant against which casirivimab/ imdevimab has sufficient efficacy

For the treatment of adolescent patients with COVID-19 who do not require supplementary oxygen, who are at increased risk of a severe course of COVID-19, and who are infected with a viral variant against which casirivimab/ imdevimab has sufficient neutralising activity, 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 supplemental oxygen and who are at increased risk for a severe course of COVID-19 (see study description for patient population b). For this age group, an additional benefit of casirivimab/ imdevimab 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 treatment of COVID-19 in adults and adolescents 12 years and older, weighing at least 40 kg, who do not require supplemental oxygen and who are at increased risk for a severe course of 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.

About patient group a):

Adults and adolescents infected with a viral variant of SARS-CoV-2 for which there is evidence or current pandemic activity of insufficient neutralising activity of casirivimab/ imdevimab, no statement on the additional benefit of casirivimab/ imdevimab in the treatment of COVID-19 is possible. For this patient population, an additional benefit of casirivimab/ imdevimab compared to the appropriate comparator therapy is not proven.

About patient group b):

For this patient group, the pharmaceutical company presents the COV-2067 study.

In the mortality category, the endpoint of overall mortality shows an advantage for casirivimab/ imdevimab. In terms of morbidity, there are statistically significant advantages in hospitalisation due to COVID-19 and in the resolution of COVID-19 symptoms. Quality of life data were not collected. No usable data are available for the endpoints in the side effects category, but no negative effects of casirivimab/ imdevimab are expected to a degree that could call into question the additional benefit of casirivimab/ imdevimab. In summary, there are positive effects in the categories of mortality and morbidity, which are not countered by negative effects.

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.

Overall, for adults infected with a viral variant for which casirivimab/ imdevimab has sufficient efficacy, a hint for a considerable additional benefit of casirivimab/ imdevimabis derived.

About patient group c):

No data are available for adolescents 12 to < 18 years old weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk for a severe course of COVID-19. For this age group, an additional benefit of casirivimab/ imdevimab 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[2], 100 % of infections in Germany are currently attributable to the Omicron variants.

The virus variants for which casirivimab/ imdevimab 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 casirivimab/ imdevimab has sufficient efficacy.

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. As the medicinal product to be assessed does not have sufficient efficacy against the currently dominant viral variants of SARS-CoV-2 based on *in vitro* neutralisation tests, no patient is currently eligible for treatment with casirivimab/ imdevimab.

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: 11 July 2022):

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

For casirivimab/ imdevimab, no sufficient efficacy could be demonstrated against variants of the Omicron virus[2] 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 both patient populations (adults and adolescents), the costs are presented together here.

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

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. The costs of the above-mentioned medicinal therapy vary from patient to patient and therefore cannot be quantified.

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				
Therapy according to doctor's instructions	Different from patient to patient			

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	600 mg	600 mg	1	1 x 600 mg
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					
Casirivimab/ imdevimab	incalculable				
Appropriate comparator therapy					
Therapy according to doctor's instructions	Different from patient to patient				

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 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				
Casirivimab/ imdevimab	Therapy with monoclonal antibodies in patients infected with the coronavirus SARS-CoV-2	1	€ 360.00	€ 360.00

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 6 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 14 September 2022 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