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
Sotrovimab (COVID-19, ≥ 12 years)

of 3 November 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 the date of resolution of 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 coronavirus disease 2019 (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 sotrovimab that the suspension requirements according to the above-mentioned resolution are met. In a letter dated 11 May 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 dossier 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.

The pharmaceutical company submitted the final dossier to the G-BA on 10 May 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 August 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a decision on whether an additional benefit of sotrovimab 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 sotrovimab.

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 Sotrovimab (Xevudy) in accordance with the product information

Xevudy is indicated for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19.

Therapeutic indication of the resolution (resolution of 03.11.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with COVID-19 disease who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which sotrovimab has a considerably reduced or insufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

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

Appropriate comparator therapy:

Therapy according to doctor's instructions

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

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

Appropriate comparator therapy:

Therapy according to doctor's instructions

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

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

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

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

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

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

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

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

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

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 ingredients remdesivir and casirivimab/ imdevimab were assessed by the G-BA as part of the early benefit assessment.

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

There is a hint of a considerable additional benefit of casirivimab/ imdevimab compared to the appropriate comparator therapy for the treatment of adult patients with COVID-19 disease who do not require oxygen therapy, who are at increased risk of severe COVID-19, and who are infected with a viral variant against which casirivimab/ imdevimab has sufficient efficacy. So far, there is only limited experience with this combination of active ingredients in care, which is why the significance cannot yet be conclusively assessed. Therefore, casirivimab/ imdevimab is not determined to be an appropriate comparator therapy for these patient groups at this time. For casirivimab/ imdevimab, no sufficient efficacy could be demonstrated against the currently dominant variants of the Omicron virus using *in vitro* neutralisation tests. Consequently, the G-BA was unable to identify an additional benefit for patients with COVID-19 disease due to infection with a viral variant against which casirivimab/ imdevimab does not have sufficient efficacy. Therefore, casirivimab/ imdevimab is not currently determined as an appropriate comparator therapy for this patient group either.

Recently, the active ingredients regdanvimab (currently unavailable in Germany), nirmatrelvir/ ritonavir and tixagevimab/ cilgavimab have been approved for the treatment of COVID-19 patients who do not require oxygen therapy 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 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, on the basis of the Federal Ministry of Health's general order of 25 March 2022 on the purchase and use of monoclonal antibodies and on the purchase and administration of antiviral oral medicinal products against COVID-19.

The clinical significance of these therapy options cannot be assessed at the present time. Also, the antiviral substances are currently only given a weak or open recommendation for special risk groups in the guidelines. Due to the limited experience with these active ingredients in the provision of care, 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 sotrovimab. 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 sotrovimab 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 sotrovimab is assessed as follows:

a) Adults with COVID-19 disease who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which sotrovimab has a considerably reduced or insufficient efficacy

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

Justification:

In the COMET-ICE study [for a description of the study, see patient population b)], information on the viral variant present was available for about two thirds of the patients. The majority of the study participants examined were infected with the wild-type virus. Other virus variants detected included the alpha variant and the epsilon variant. In accordance with the infection incidence at the time of study implementation (August 2020 to September 2021), neither the delta nor the Omicron variant was detected in the study participants examined. Sotrovimab shows significantly reduced efficacy compared to the Omicron virus variants circulating alone in Germany at the time of passing the resolution (demonstrated by in vitro neutralisation tests). Due to this significantly reduced efficacy, the effects observed in the COMET-ICE study are not transferable to patients infected with the virus variants Omicron BA.2, BA.2.12.1, BA.4 or BA.5 circulating at the time of the benefit assessment.

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

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

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

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

Justification:

For the benefit assessment, the pharmaceutical company submits the VIR-7831-5001 study (214367; COMET-ICE).

The COMET-ICE study is a placebo-controlled, double-blind, randomised study on outpatient treatment with sotrovimab in adult patients with early-stage COVID-19 disease. Symptomatic patients with confirmed SARS-CoV-2 infection detected by either reverse transcriptase polymerase chain reaction (RT-PCR) test or antigen test ≤ 7 days prior to screening were enrolled in the study. Symptoms had to have started ≤ 5 days prior to enrolment in the study. Furthermore, COVID-19 patients had to have at least one pre-existing risk factor for disease progression to hospitalisation or be ≥ 55 years of age. However, patients with severe immunosuppression or immunosuppressive therapy including cancer treatment were excluded from the study. In the study, only outpatient treatment with sotrovimab was examined. In addition, only patients without vaccination protection against SARS-CoV-2 were considered.

A total of 1,057 patients were randomly assigned to treatment with sotrovimab or placebo in a 1:1 ratio across both phases in the study.

The primary endpoint of the study was the combined endpoint of hospitalisation for any cause or death from any cause until day 29. Patient-relevant secondary endpoints were overall mortality and endpoints for morbidity, health-related quality of life and adverse events (AEs). Follow-up was up to 24 weeks according to the study design for each endpoint.

Implementation of the appropriate comparator therapy

In the COMET-ICE study, the use of approved or antiviral agents and monoclonal antibodies against SARS-CoV-2 under investigation was not allowed or they were not used. In particular, anti-inflammatory and analgesic active ingredients were administered as concomitant therapies for the treatment of COVID-19 in the COMET-ICE study. Despite the increasing availability and use of antivirals and monoclonal antibodies, the concomitant treatment with anti-inflammatory and analgesic agents in the COMET-ICE study currently represents, in the view of the G-BA, an overall sufficient implementation of the appropriate comparator therapy in the present therapeutic indication.

Transferability to the current pandemic situation in Germany

Patients with at least one vaccination against SARS-CoV-2 were excluded from the COMET-ICE study. In contrast, at the time of the benefit assessment, a large percentage of the population already has sufficient immunisation through adequate vaccination protection and/or past exposure to the virus. Immunisation significantly reduces the risk of progression to severe

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

Furthermore, the Omicron virus variants, in which the risk of a severe course of COVID-19 disease and the observed number of hospitalisations are significantly lower, were not detected in the study participants examined, in accordance with the infection history at the time the study was carried out.

Despite the major uncertainties described here, the transfer of the results from the unvaccinated patients enrolled in the COMET-ICE 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 sotrovimab 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 sotrovimab.

Morbidity

Development of severe and/or critical respiratory COVID-19 by day 29
The development of severe and/or critical respiratory COVID-19 was operationalised in the COMET-ICE study via the need for supplemental oxygen using either a low-flow nasal cannula/ face mask (category 2) and high-flow oxygen devices or non-invasive ventilation (category 3) and mechanical ventilation/ extracorporeal membrane oxygenation (ECMO) (category 4) until day 29. Categories 2 and 3 were classified as severe and category 4 as critical. The study documents did not further define the decision on the type of supplemental oxygen to be administered. It is assumed that the decision was at the discretion of the attending physician. For the endpoint of development of severe and/or critical respiratory COVID-19, there is a statistically significant difference between treatment groups to the advantage of sotrovimab.

Hospitalisation of any duration due to non-respiratory complications from COVID-19 by day 29 and hospitalisation > 24 h for any cause
In the dossier, the pharmaceutical company presents various evaluations of hospitalisation, each of which is based on a different duration of hospitalisation.

Regarding operationalisation, the study documents indicate that hospitalisation of any duration due to non-respiratory complications of COVID-19 was primarily for cardiac, renal, neurological or haematological events. Patients who developed severe and/or critical respiratory COVID-19 during the course of the study and were hospitalised for this reason, if applicable, were recorded using a separate endpoint according to the study design. Further information on the operationalisation of the endpoint of hospitalisation of any duration due to non-respiratory complications of COVID-19 is not available in the dossier. It is assumed that the hospitalisation was at the discretion of the attending physician.
For the benefit assessment, in addition to the endpoint of development of severe and/or critical respiratory COVID-19, hospitalisation of any duration due to non-respiratory complications of COVID-19 will be used to represent events that represent severe disease progression.
For the endpoint of hospitalisation of any duration due to non-respiratory complications of COVID-19, there is no statistically significant difference between the treatment groups.
Furthermore, the results on the percentage of patients with hospitalisation with a minimum duration > 24 h for any cause are used. For hospitalisation with a minimum duration > 24 h for any cause, there is a statistically significant difference between the treatment groups to the advantage of sotrovimab.
In view of the fact that the endpoint "The results for hospitalisation of any duration for any cause" is a different operationalisation of the endpoint of hospitalisation for any cause, this does not result in any further usable information. Therefore, the results on this were only presented additionally.

Admission to an intensive care unit for any cause by day 29
The endpoint "admission to an intensive care unit for any cause" represents a further operationalisation of the disease progression and is therefore used for the benefit assessment. For the endpoint of admission to an intensive care unit for any cause, there is a statistically significant difference between the treatment groups to the advantage of sotrovimab.

Quality of life

SF-12 hybrid
In the COMET-ICE study, health-related quality of life was assessed using the SF-12 hybrid. The pharmaceutical company's dossier shows that the instrument SF-12 extended is the Short Form-36 Health Survey (SF-36) domains of vitality and physical role functioning. The pharmaceutical company does not present the SF-12 hybrid questionnaire in the dossier, nor does it provide information on the validity of the instrument. However, based on the available information, it is assumed that a validated version of the SF-12 with a corresponding extension was used as the SF-12 hybrid in the study. However, the validity of the extended form has not been demonstrated by the pharmaceutical company. Irrespective of the validity of the extension, evaluations of the SF-12 without the extensions that would be relevant for the present benefit assessment would in principle be possible under these conditions.
However, the dossier shows that there were very low responses to the SF-12 hybrid in the study, which decreased sharply early on in the course of the study. The evaluations for the SF-12 hybrid submitted by the pharmaceutical company are therefore not usable for the present benefit assessment.

Side effects

SAEs, severe AEs and discontinuations due to AEs
For the endpoints of SAEs and severe AEs, there is no statistically significant difference between the treatment groups. No events occurred in the endpoint of discontinuation due to AEs.

Infusion-related reactions (AEs and SAEs)
According to the product information, the infusion of sotrovimab is to be administered over 30 minutes. In contrast, in the study, the administration was planned over a duration of 1 h. The extent to which the longer infusion duration might influence the occurrence of infusion-related reactions remains unclear. For the endpoint of infusion-related reactions (AEs), there is no statistically significant difference between the treatment groups. No events occurred in the endpoint of infusion-related reactions (SAEs).

Overall assessment

For the benefit assessment, the double-blind, randomised controlled trial COMET-ICE is available, which compared sotrovimab versus placebo in non-hospitalised patients in the early phase of COVID-19 disease who did not require oxygen therapy.
In the mortality category, there was a statistically significant difference between the treatment groups for the endpoint of overall mortality to the advantage of sotrovimab.
In the morbidity category, there were statistically significant advantages in favour of sotrovimab compared to the control arm for the endpoints "development of severe and/or critical respiratory COVID-19", "hospitalisation > 24 h for any cause" and "admission to an intensive care unit for any cause". For the other endpoint of the morbidity category, hospitalisation of any duration due to non-respiratory complications of COVID-19, there is no statistically significant difference between the treatment groups.
In the category of health-related quality of life, no usable data are available for the SF-12 hybrid endpoint on health-related quality of life.
For the endpoints in the side effects category, there are neither advantages nor disadvantages of sotrovimab.
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, "development of severe and/or critical respiratory COVID-19" and "admission to an intensive care unit for any cause", a considerable additional benefit is derived for adults with COVID-19 disease for the treatment of infections with a viral variant for which sotrovimab has sufficient neutralisation activity, compared to therapy according to doctor's instructions.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on the randomised, double-blind COMET-ICE 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 endpoints of serious adverse events (SAEs) and severe AEs.
Regardless of this, uncertainties remain regarding the transferability of the study results to the German healthcare context. The transfer of the results from the unvaccinated patients enrolled in the COMET-ICE study to patient groups who do not achieve complete immunisation despite vaccination or who have complex risk factors despite immunocompetence and complete vaccination is possible in principle. However, it remains

unclear whether the observed effects of the unvaccinated patients can be transferred to these patient groups without restriction. The reliability of the study data for the present research question is therefore reduced overall. Overall, therefore, relevant uncertainties remain with regard to transferability to the German healthcare context, which in the overall assessment of the reliability of data justify the derivation of a hint for an additional benefit.

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

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

Justification:

No data are available for adolescents 12 to < 18 years old weighing at least 40 kg who do not require oxygen therapy and who are at increased risk for a severe course of COVID-19 (see study description for patient population b). Since no data is available, no differentiated statement can be made on the effect on the different viral variants. For this age group, an additional benefit of sotrovimab is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Xevudy with the active ingredient sotrovimab. Sotrovimab 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.

The pharmaceutical company submits the COMET-ICE study for the benefit assessment.

Treatment with sotrovimab is currently not considered as a rule since sotrovimab shows significantly reduced efficacy against the currently dominant viral variants of SARS-CoV-2 based on *in vitro* neutralisation tests.

About patient group a):

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

About patient group b):

In the mortality category, the endpoint of overall mortality shows an advantage for sotrovimab. For morbidity, there are statistically significant advantages for the endpoints "development of severe and/or critical respiratory COVID-19", "hospitalisation > 24 h for any

cause" and "admission to an intensive care unit for any cause" in favour of sotrovimab compared to the control arm.

Quality of life data submitted was not usable for the benefit assessment. For the endpoints in the side effects category, there are neither advantages nor disadvantages of sotrovimab. 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.

In the overall assessment, a hint of a considerable additional benefit of sotrovimab over a therapy according to doctor's instructions is derived for adults infected with a viral variant for which sotrovimab has sufficient efficacy.

About patient group c):

No data is available in the COMET-ICE study 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 sotrovimab 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 sotrovimab has sufficient or significantly limited 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 viral variants for which sotrovimab 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 sotrovimab has a significantly limited efficacy.

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

Treatment with sotrovimab is currently not considered as a rule since the medicinal product to be assessed against the currently dominant viral variants of SARS-CoV-2 shows a significantly reduced efficacy based on in vitro neutralisation tests. Only in patients with relevant immunosuppression and/or prolonged viral excretion, the use of sotrovimab as combination therapy with antivirals can be considered in individual cases.

[2] RKI weekly situation report on the coronavirus disease-2019 (COVID-19) (20.10.2022)

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 Xevudy (active ingredient: sotrovimab) at the following publicly accessible link (last access: 25 October 2022):

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

For sotrovimab, a significantly reduced 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. This variant was not investigated in the pivotal COMET-ICE study. The majority of the study participants examined were infected with the wild-type virus and other virus variants detected included the alpha variant and the epsilon variant.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information from the pharmaceutical company in the benefit assessment dossier.

Sotrovimab is not listed in the LAUER-TAXE®. The price of the medicinal product is therefore taken from the information provided by the pharmaceutical company in the benefit assessment dossier. In Module 3 of its dossier, the pharmaceutical company states a pharmacy sales price of € 3,169.67, including 19% value added tax.

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				
Sotrovimab	1 x daily	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					
Sotrovimab	500 mg	500 mg	1 x 500 mg	1	1 x 500 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					
Sotrovimab 500 mg	1 CIS	€ 3,169.67	€ 1.77	€ 177.73	€ 2,990.17
Appropriate comparator therapy					
Therapy according to doctor's instructions	Different from patient to patient				

Information of the pharmaceutical company

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 sotrovimab, a uniform flat-rate remuneration for services provided by SHI-accredited physicians is granted in accordance with the Monoclonal Antibody Regulation (MAKV; valid till 7 April 2023). The reimbursement for the administration of sotrovimab 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				
Sotrovimab	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 27 October 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the marketing authorisation was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 17 May 2022.

On 10 May 2022, the pharmaceutical company submitted a dossier for the benefit assessment of sotrovimab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 13 May 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient sotrovimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 August 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 15 August 2022. The deadline for submitting written statements was 5 September 2022.

The oral hearing was held on 26 September 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 25 October 2022, and the proposed resolution was approved.

At its session on 3 November 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 October 2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	17 May 2022	New determination of the appropriate comparator therapy
Working group Section 35a	21 September 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	26 September 2022	Conduct of the oral hearing
Working group Section 35a	5 October 2022 19 October 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	25 October 2022	Concluding discussion of the draft resolution
Plenum	3 November 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 November 2022

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

Prof. Hecken