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
Nirmatrelvir/ Ritonavir (COVID-19)

of 15 December 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

On the date of resolution of 20 January 2022, the G-BA decided on an exemption to temporarily suspend the obligation to submit the dossier for the benefit assessment procedure of the medicinal product Paxlovid for the treatment of coronavirus disease 2019 (COVID-19), which is in a so-called "rolling review" procedure of the European Medicines Agency (EMA) at the prevailing very high risk posed by COVID-19 to public health in Germany. The pharmaceutical company was requested 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 28 June 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 4 October 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/ nirmatrelvir/ ritonavir 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 nirmatrelvir/ ritonavir.

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 Nirmatrelvir/ Ritonavir (Paxlovid) according to the product information

Paxlovid is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

Therapeutic indication of the resolution (resolution of 15 December 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19

Appropriate comparator therapy for nirmatrelvir/ ritonavir:

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

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

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, sotrovimab 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, without the need for supplemental oxygen and with an increased risk of progressing to severe COVID-19, no non-medicinal treatments are indicated.

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

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

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

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.

An overwhelming 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, casirivimab/ imdevimab and sotrovimab 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 who are at increased risk for progressing to severe 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 group.

A hint for a considerable additional benefit of casirivimab/ imdevimab was identified for the treatment of adult patients with COVID-19, who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, and who are infected with a viral variant against which casirivimab/ imdevimab has sufficient efficacy. The viral variants against which casirivimab/ imdevimab has sufficient efficacy are currently no longer circulating. For casirivimab/ imdevimab, no sufficient efficacy could be demonstrated against the currently dominant variants of the Omicron virus using in vitro neutralisation tests. Consequently, the G-BA was unable to identify an additional benefit for patients with COVID-19 due to infection with a viral variant against which casirivimab/ imdevimab does not have sufficient efficacy. Therefore, casirivimab/ imdevimab is not determined to be an appropriate comparator therapy for nirmatrelvir/ ritonavir at this time. A hint for a considerable additional benefit of sotrovimab was identified for the treatment of adult patients with COVID-19, who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, and who are infected with a viral variant against which sotrovimab has sufficient efficacy. The viral variants against which sotrovimab has sufficient efficacy are currently no longer circulating. For sotrovimab, only a significantly reduced efficacy could be demonstrated against the currently dominant variants of the Omicron virus using in vitro neutralisation tests. Consequently, the G-BA was unable to identify an additional benefit for patients with COVID-19 due to infection with a viral variant against which sotrovimab only has a significantly reduced or insufficient efficacy. Therefore, sotrovimab is not determined to be an appropriate comparator therapy for nirmatrelvir/ ritonavir at this time.

Recently, the active ingredients regdanvimab (currently unavailable in Germany) 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 supplemental oxygen and who 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 no longer addressed by the present

therapeutic indication for starting treatment with nirmatrelvir/ ritonavir. 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 nirmatrelvir/ ritonavir for the 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.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nirmatrelvir/ ritonavir is assessed as follows:

<u>Adults with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19</u>

Hint for a considerable additional benefit

Justification:

The pharmaceutical company presents the EPIC-HR study for the assessment of the additional benefit of nirmatrelvir/ ritonavir. In addition, the pharmaceutical company submits evaluations of the EPIC-SR study within the framework of the written statement procedure.

EPIC-HR

The EPIC-HR study is a placebo-controlled, double-blind, randomised study of outpatient treatment with nirmatrelvir/ ritonavir in adult patients in the early phase of COVID-19 who had ≥ 1 risk factor for progressing to severe COVID-19. Symptomatic patients with confirmed SARS-CoV-2 infection detected by polymerase chain reaction (PCR) test ≤ 5 days prior to randomisation were enrolled in the study. The assessment report of the European Medicines Agency shows that 99% of the patients were infected with the Delta variant. In the study, only outpatient treatment with nirmatrelvir/ ritonavir was examined. In addition, only patients without vaccination protection against SARS-CoV-2 were considered.

Moreover, only a few patients with complex risk factors were enrolled in the EPIC-HR study. In addition, patients with a previous, molecularly confirmed SARS-CoV-2 infection were excluded from the EPIC-HR study. However, about half of the patients enrolled in the study had a positive serostatus at the start of the study despite these limitations according to the inclusion criteria.

A total of 2,246 patients were assigned to treatment with nirmatrelvir/ ritonavir or placebo in a 1:1 ratio in the study. Randomisation was stratified by region and by treatment or planned treatment with monoclonal antibodies against COVID-19.

The primary endpoint of the study was the combined endpoint of hospitalisation due to COVID-19 or death from any cause until day 28. Patient-relevant secondary endpoints were overall mortality, endpoints on morbidity and adverse events (AEs). Follow-up was up to 24 weeks according to the study design for each endpoint.

Relevant sub-population

Patients with ≥ 1 risk factor for progressing to severe COVID-19 were enrolled in the EPIC-HR study. However, the risk factors defined in the inclusion criteria did not fully correspond to the risk factors defined by the Robert Koch Institute (RKI). The RKI sees an increased risk of progressing to severe COVID-19 only from a body mass index (BMI) of > 30. Based on this, the pharmaceutical company formed the RKI modified Intention-To-Treat 2 (RKI-mITT2) population for the present benefit assessment, which defines a BMI of ≥ 30 as a risk factor. Patients in this sub-population had to have at least 1 specific previous disease (e.g. immunosuppressive disease or cardiovascular disease) or be taking immunocompromising drugs, or be ≥ 60 years of age or have a BMI of ≥ 30, or smoke. The relevant sub-population comprised 1,908 patients.

Implementation of the appropriate comparator therapy

In the EPIC-HR study, approved or investigational antiviral active ingredients and monoclonal antibodies against SARS-COV-2 were not used or were used only to a limited extent. In particular, anti-inflammatory and analgesic active ingredients were administered as concomitant therapies for the treatment of COVID-19 in the EPIC-HR study. Despite the increasing availability and use of antivirals and monoclonal antibodies, the concomitant treatment with anti-inflammatory and analgesic agents in the EPIC-HR 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 EPIC-HR 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 is therefore considered as a whole, regardless of the vaccination status.

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

EPIC-SR

In the written statement procedure, the pharmaceutical company submitted evaluations of a sub-population of the EPIC-SR study and meta-analytically summarised them with results of the EPIC-HR study. However, the pharmaceutical company does not submit a complete preparation of the data according to module templates. Irrespective of this, it is questionable whether the patients included in the sub-population correspond to a relevant percentage of the present therapeutic indication. The majority (70%) of the sub-population are fully vaccinated patients according to the pharmaceutical company's statement, whereby full immunisation reduces the risk of progressing to severe COVID-19 according to the definition of the Standing Committee on Vaccination. Accordingly, these patients may not be covered by the present therapeutic indication, as there is no increased risk of severe disease progression. Nor can it be deduced from the available information that patients with incomplete immunisation, with relevant risk of inadequate vaccine response or complex risk factors were included for whom there is an increased risk of severe disease progression despite complete vaccination. In addition, patients with an immunosuppressive disease or a prolonged treatment with an immunosuppressive therapy were not allowed to participate in the EPIC-SR study according to exclusion criteria.

For the reasons mentioned above, the EPIC-SR study is not used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

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

Morbidity

Severe COVID-19
The endpoint "severe COVID-19" was operationalised in the EPIC-HR study as > 24 hours of acute care in a hospital or similar acute care facility. For the present benefit assessment, the endpoint of severe COVID-19 operationalised as hospitalisation due to COVID-19 is used. It is assumed that the hospitalisation was at the discretion of the attending physician. Based on the data on the percentage of patients requiring supplemental oxygen, it is also assumed that hospitalisation due to COVID-19 is a sufficient approximation of the occurrence of severe disease progression.
For the endpoint "severe COVID-19", there is a statistically significant difference between the treatment groups to the advantage of nirmatrelvir/ ritonavir.

Need for intensive medical care due to any cause
The endpoint "need for intensive medical care due to any cause" represents a further operationalisation of the disease progression and is therefore used for the benefit assessment. For the endpoint "need for intensive medical care due to any cause", there is a statistically significant difference between the treatment groups to the advantage of nirmatrelvir/ ritonavir.

Relief of COVID-19 symptoms until day 28
For the EPIC-HR study, 14 COVID-19 symptoms (including myalgia, shortness of breath, chills, cough) were recorded daily for 28 days using a digital patient diary. In the survey of symptoms, their severity grade was estimated on a 4-point Likert scale in which a value of 0 corresponds to no occurrence of the corresponding symptom and values of 1, 2 and 3 correspond to a mild, moderate or severe grade of severity of the respective symptom, respectively. The pharmaceutical company submits both evaluations of the time to reduction of each COVID-19 symptom recorded and evaluations of the time to reduction of all symptoms in total. For this benefit assessment, the time to reduction of all symptoms is used. Reduction of COVID-19 symptoms was operationalised as the event that occurred on the first of 4 consecutive days on which all symptoms that were classified as moderate (2) or severe (3) at study entry, classified as mild (1) or absent (0), and all symptoms classified as mild (1) or absent (0) at study entry were classified as absent (0). The first day of the period of 4 consecutive days was considered the time of the event.
For the endpoint "reduction of COVID-19 symptoms by day 28", there is a statistically significant difference between the treatment groups to the advantage of nirmatrelvir/ ritonavir.

COVID-19 symptoms at week 24
In addition, COVID-19 symptoms were collected by telephone at the end of the study after 24 weeks. In this survey, in addition to the 14 symptoms, concentration difficulties, sleep disorders, palpitations and other symptoms were evaluated.
For the endpoint "COVID-19 symptoms at week 24", there is no statistically significant difference between the treatment groups.

Activity impairment (WPAI-COVID-19), health status (EQ-5D VAS)
The endpoints "activity impairment" assessed by question 6 of the WPAI-COVID-19 and "health status" assessed by the VAS of the EQ-5D are patient-relevant and are used for the benefit assessment. Health status assessed using the VAS of the EQ-5D should be collected at day 1, day 5, day 14, day 34 and at the follow-up at week 12 and week 24. The endpoint of activity impairment (WPAI-COVID-19) was collected at day 5 and day 14 and at week 12 and week 24.
For both endpoints, the return rates at the beginning of the survey are very low at about 3% each. Although the return rates increase at later survey dates, they remain at a low level of less than 45% in each case. Consequently, only very few patients are included in the evaluations, so that no usable data are available for the benefit assessment.

Quality of life

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

Side effects

For the endpoints of the category side effects, no usable data are available. When collecting data on SAEs, severe AEs and discontinuations due to AEs, disease-related events were included to a relevant extent in the EPIC-HR study. This is also indicated by the fact that more events occurred in the placebo arm than in the verum arm.
Overall, there are thus no usable data for assessing the side effects of nirmatrelvir/ ritonavir. However, based on the results on frequent SAEs, severe AEs and discontinuations due to AEs, no adverse effects of nirmatrelvir/ ritonavir are expected to the degree that could question the additional benefit of nirmatrelvir/ ritonavir.

Overall assessment

For the benefit assessment, the double-blind, randomised controlled trial EPIC-HR is available, which compared nirmatrelvir/ ritonavir versus placebo in non-hospitalised patients in the early phase of COVID-19, without the need for supplemental oxygen and with an increased risk of progressing to severe COVID-19.
In the mortality category, there is a statistically significant difference between the treatment groups for the endpoint of overall mortality to the advantage of nirmatrelvir/ ritonavir.
In the morbidity category, the endpoints "severe COVID-19", "need for intensive medical care due to any cause" and "reduction of COVID-19 symptoms by day 28" show statistically significant advantages in favour of nirmatrelvir/ ritonavir compared to the control arm. For the other endpoint of the morbidity category "COVID-19 symptoms at week 24", there is no statistically significant difference between the treatment groups. No usable data are available for the morbidity endpoints "activity impairment (WPAI-COVID-19)" and "health status (EQ-5D VAS)".
Endpoints for the health-related quality of life category 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, severe SAEs and discontinuations due to AEs, no adverse effects of nirmatrelvir/ ritonavir are expected to the degree that could question the additional benefit of nirmatrelvir/ ritonavir.
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 "overall mortality", "severe COVID-19", "need for intensive medical care due to any cause" and

"reduction of COVID-19 symptoms by day 28", a considerable additional benefit is derived 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 EPIC-HR study.
The risk of bias is classified as low at study level. The endpoint-specific risk of bias is considered low for the results on all usable endpoints except the endpoint "reduction of COVID-19 symptoms by day 28".
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 EPIC-HR 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. Furthermore, there are uncertainties regarding the transferability to the current healthcare context with regard to the viral variants in terms of disease progression, as the currently circulating variant is Omicron, while in the study the vast majority of patients were infected with the Delta variant.
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.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Paxlovid with the combination of active ingredients nirmatrelvir/ ritonavir. Nirmatrelvir/ ritonavir is approved for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The appropriate comparator therapy was determined to be a therapy according to doctor's instructions.

For this patient group, the pharmaceutical company is presenting the EPIC-HR study, which is investigating nirmatrelvir/ ritonavir in comparison with placebo in patients with early-stage COVID-19 disease.

In the mortality category, the endpoint of overall mortality shows an advantage of nirmatrelvir/ ritonavir. For morbidity, there are statistically significant advantages for the endpoints "severe COVID-19," "need for intensive medical care due to any cause" and "reduction of COVID-19 symptoms by day 28" in favour of nirmatrelvir/ ritonavir compared with the control arm.

No data are available for the endpoint category of health-related quality of life. Side effects data submitted were not usable for the benefit assessment.

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, there is a hint for a considerable additional benefit of nirmatrelvir/ ritonavir compared to a therapy according to doctor's instructions.

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 resolution is based on the information from the dossier assessment of the IQWiG for remdesivir (mandate A22-04).

Since the percentage value for the criterion "increased risk of progressing to severe COVID-19" for the upper limit of patient numbers estimated in the dossier on nirmatrelvir/ ritonavir presumably represents a clear overestimation, it can be assumed that the true patient number is closer to the upper limit from the dossier on remdesivir (approx. 1.3 million) than to the upper limit from the dossier on nirmatrelvir/ ritonavir (approx. 13.8 million).

It can also be assumed that the true value for the lower limit is closer to the value given in the dossier on remdesivir (approx. 218,000) than to the value from the dossier on nirmatrelvir/ ritonavir (approx. 44,500), as it is closer to the RKI data on hospitalisation cases associated with COVID-19 in 2022. Overall, using the figures from the resolution on remdesivir seems appropriate.

However, patient numbers are subject to massive uncertainty due to insufficiently predictable influences such as variants of SARS-CoV-2, immunity and population protection measures.

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 Paxlovid (combination of active ingredients: nirmatrelvir/ ritonavir) at the following publicly accessible link (last access: 29 September 2022):

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

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

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.

Nirmatrelvir/ ritonavir is currently not listed with the pharmaceutical company Pfizer as distributor 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 indicates a manufacturer's selling

price (SPC/HAP) of € 900 and a taxe-sales (total) of € 1,149.16. Nirmatrelvir/ ritonavir is currently listed with the Federal Ministry of Health as the distributor in the LAUER-TAXE® under a different price. The indicated price results from the regulations of the SARS-CoV-2 Pharmaceutical Price Ordinance and is not charged to the statutory health insurance.

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				
Nirmatrelvir/ ritonavir	2 x daily	1	5.0	5.0
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					
Nirmatrelvir/ ritonavir	300 mg/ 100 mg	600 mg/ 200 mg	4 x 150 mg/ 2 x 100 mg	5.0	20 x 150 mg/ 10 x 100 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					
Nirmatrelvir/ ritonavir	30 FCT	€ 1,149.16	€ 1.77	€ 63.00	€ 1,084.39
Appropriate comparator therapy					
Therapy according to doctor's instructions	Different from patient to patient				
Abbreviation: FCT = film-coated tablets					

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.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

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

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

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

Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

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

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 7 December 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 June 2022, the pharmaceutical company submitted a dossier for the benefit assessment of nirmatrelvir/ ritonavir to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 June 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 combination of active ingredients nirmatrelvir/ ritonavir.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 September 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 4 October 2022. The deadline for submitting written statements was 25 October 2022.

The oral hearing was held on 7 November 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 6 December 2022, and the proposed resolution was approved.

At its session on 15 December 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 December 2021	Determination of the appropriate comparator therapy
Working group Section 35a	2 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 November 2022	Conduct of the oral hearing,
Working group Section 35a	16.11.2022; 30.11.2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 December 2022	Concluding discussion of the draft resolution
Plenum	15 December 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 December 2022

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

Prof. Hecken