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
Remdesivir (new therapeutic indication: COVID-19, not requiring supplemental oxygen, increased risk of progressing to severe COVID-19)

of 7 July 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient remdesivir (Veklury) was listed for the first time on 1 June 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 20 December 2021, Veklury received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 14 January 2022, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure

(VerfO) of the G-BA on the active ingredient remdesivir with the new therapeutic indication (treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19).

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 19 April 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 remdesivir compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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 remdesivir.

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 remdesivir (Veklury) in accordance with the product information

Veklury 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 of progressing to severe COVID-19.

Therapeutic indication of the resolution (resolution of 07.07.2022):

See new therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with COVID-19 disease who do not require supplemental oxygen 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

[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.

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

on 1. Casirivimab/ imdevimab, regdanvimab, sotrovimab and nirmatrelvir/ ritonavir 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. Resolution on the benefit assessment of remdesivir according to Section 35a SGB V of 16 September 2021.

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 disease 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 disease. 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.

Recently, the active ingredients casirivimab/ imdevimab, regdanvimab, sotrovimab and nirmatrelvir/ ritonavir have been approved for the treatment of COVID-19 patients who do not require supplementary 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 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 remdesivir. 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 with severe ($SpO_2 < 90\%$, respiratory rate > 30/min) or critical (ARDS, sepsis, ventilation, vasopressor administration) COVID-19 disease. As this concerns later treatment settings, it is not included in the appropriate comparator therapy derived for the present therapeutic indication.

In the overall view 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 remdesivir. Therapy, according to doctor's instructions, is understood to be the therapy that ensures the best possible, patient-individually optimised treatment of COVID-19 disease. 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 remdesivir is assessed as follows:

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

Hint for a minor additional benefit

Justification:

The pharmaceutical company presents the GS9012 (PINETREE) study for the assessment of the additional benefit of remdesivir.

The GS9012 study is a placebo-controlled, double-blind, randomised phase 3 study on outpatient treatment with remdesivir in patients with early-stage COVID-19 disease. Symptomatic patients with confirmed COVID-19 disease who did not require or were not expected to receive supplemental oxygen and who had at least one pre-existing risk factor for disease progression to even hospitalisation or were ≥ 60 years of age were enrolled in the study. Only patients without vaccination protection were included in the study; patients who had received at least one vaccination against SARS-CoV-2 were excluded from the study. A total of 584 patients were randomly assigned in a 1:1 ratio to treatment with remdesivir (N = 292) or placebo (N = 292), with only 279 vs 283 patients (intervention vs control arm) receiving at least one treatment. The study was conducted predominantly in study sites in the USA and was terminated before reaching the planned number of cases (n = 1264) due to the decrease in new cases, increased availability of monoclonal antibodies as an alternative to placebo and increased vaccination in high-risk patients.

Implementation of the appropriate comparator therapy
In the GS9012 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 GS9012 study. The concomitant treatment with anti-inflammatory and analgesic active ingredients in the GS9012 study represents an overall sufficient implementation of the appropriate comparator therapy.

Transferability to the current situation in Germany
Patients with at least one vaccination against SARS-CoV-2 were excluded from the GS9012 study. In addition, no information on the serostatus of the patients is available in the study. In contrast, at the time of the benefit assessment, a large percentage of the population already has sufficient immunisation either through adequate vaccination protection or through past infection. 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, it is unclear with which viral variant the enrolled patients were infected. The virus variant Omicron, which was widely used at the time of the benefit assessment and for

which the risk of progressing to severe COVID-19 and the observed number of hospitalisations is significantly lower, was not yet available at the time the study was conducted.

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

Extent and probability of the additional benefit

Mortality

Overall mortality
There were no deaths in the course of the study.

Morbidity

Total hospitalisation
For the endpoint "total hospitalisation", fewer statistically significant hospitalisations occurred in the remdesivir arm compared to the control arm. The observed advantage can be attributed to hospitalisation due to COVID-19.
Hospitalisation in the study was at the discretion of the principal investigator and no clear criteria for hospitalisation were given. In addition, the endpoint "total hospitalisation" was not pre-specified.

The transferability of the advantage in total hospitalisation and its interpretability for the German healthcare context is made more difficult by the fact that patients in Germany are admitted as inpatients for application with remdesivir, regardless of their clinical symptomatology.
Hospitalisation due to COVID-19
For the endpoint "hospitalisation due to COVID-19", there were fewer statistically significant hospitalisations in the remdesivir arm compared to the control arm.
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 specific case.

Need for intensive care due to any cause
For the endpoint "need for intensive care due to any cause", there is no statistically significant difference between the treatment groups.

Quality of life

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

Side effects

SAEs
For the endpoint of “SAEs, no statistically significant difference was detected between the treatment groups.

Severe AEs

For the endpoint "severe AEs" no statistically significant difference was detected between the treatment groups.

Discontinuation due to AEs
There were no discontinuations due to AEs in the course of the study.

Overall assessment
The placebo-controlled, double-blind, randomised GS9012 study on outpatient treatment with remdesivir in symptomatic, unvaccinated patients in the early stage of COVID-19 disease who do not require supplemental oxygen and who are at an increased risk of progressing to severe COVID-19 is available for the benefit assessment.

There were no deaths in the study. For the mortality category, no statement on additional benefit can be derived.

In the morbidity category, there was a statistically significant advantage of remdesivir compared to the control arm for the endpoint of total hospitalisation or hospitalisation due to COVID-19. For the other endpoint of the morbidity category, need for intensive care due to any cause, there is no statistically significant difference between the treatment groups.

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

In the category of side effects, there are no statistically significant differences between the treatment arms for the endpoints of SAEs and severe AEs. There were no therapy discontinuations due to AEs in the course of the study.

In summary, there is a positive effect in the category of morbidity which can be classified as low in magnitude.

Reliability of data (probability of additional benefit)

The risk of bias across all endpoints is rated as low for the GS9012 study.
Overall, there are uncertainties regarding the transferability to the current healthcare context with regard to the virus variants as well as the changed immune status in the course of the pandemic. Furthermore, there are uncertainties in the operationalisation of the endpoint of total hospitalisation. Due to these uncertainties, the reliability of data is classified under the "hint" category.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient remdesivir. The therapeutic indication assessed here is "for the treatment of coronavirus disease 2019 (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 GS9012 study, which is investigating remdesivir in comparison with placebo in patients with early-stage COVID-19 disease.

No deaths occurred.

With regard to morbidity, there is a statistically significant advantage of remdesivir in the endpoint "total hospitalisation" or "hospitalisation due to COVID-19".

No data are available for the endpoint category of health-related quality of life.

In the category of side effects, the endpoints "serious AEs" and "SAEs" do not show any relevant differences between the treatment groups for the benefit assessment.

There are uncertainties regarding the transferability of the study results to the German healthcare context on the one hand and to patients with infections with the currently prevailing Omicron variant as well as future variants of the SARS-COV-2 virus on the other.

In the overall assessment of the positive effect on total hospitalisation or hospitalisation due to COVID-19, taking into account the uncertainties mentioned above, a hint for a minor additional benefit is identified.

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 (mandate A22-04).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which, however, are associated with massive uncertainties 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 Veklury (active ingredient: remdesivir) at the following publicly accessible link (last access: 29 March 2022):

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

This medicinal product was authorised 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.

Remdesivir should only be used in clinical settings where patients can be closely monitored.

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 (vaccinated and unvaccinated), the costs are presented together here.

Remdesivir is listed in LAUER-TAXE® as a clinic pack only. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung), and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack plus 19 % value-added tax, in deviation from the LAUER-TAXE® data usually taken into account. In Module 3 of its benefit assessment dossier, the company specifies a hospital pharmacy purchase price of € 460.00 excluding 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				
Remdesivir	1 x daily	1	3	3
Appropriate comparator therapy				
Therapy according to doctor's instructions	Different from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Remdesivir	100 mg	Initial dose: 200 mg Maintenance dose: 100 mg	Initial dose: 2 x 100 mg Maintenance dose: 1 x 100 mg	4	4 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 (sales price of the pharmaceutical company)	Value-added tax	Costs after deduction of statutory rebates
Medicinal product to be assessed				

Designation of the therapy	Packaging size	Costs (sales price of the pharmaceutical company)	Value-added tax	Costs after deduction of statutory rebates
Remdesivir 100 mg	1 PIC	€ 460	€ 87.40	€ 547.40
Appropriate comparator therapy				
Therapy according to doctor's instructions	Different from patient to patient			
Abbreviation: PIC = powder for the preparation of an infusion solution concentrate				

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.

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 25 January 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

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

By letter dated 18 January 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 remdesivir.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 April 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 19 April 2022. The deadline for submitting written statements was 10 May 2022.

The oral hearing was held on 23 May 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 28 June 2022, and the proposed resolution was approved.

At its session on 7 July 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 January 2022	Determination of the appropriate comparator therapy
Working group Section 35a	17 May 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	23 May 2022	Conduct of the oral hearing,
Working group Section 35a	31 May 2022 14 June 2022 21 June 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	28 June 2022	Concluding discussion of the draft resolution
Plenum	7 July 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 7 July 2022

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

Prof. Hecken