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, < 18 years, ≥ 40 kg)

of 6 April 2023

**Contents**


**1. Legal basis ... 2**

**2. Key points of the resolution ... 2**

**2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy ... 3**

2.1.1 Approved therapeutic indication of Remdesivir (Veklury) in accordance with the product information ... 3

2.1.2 Appropriate comparator therapy ... 3

2.1.3 Extent and probability of the additional benefit ... 6

2.1.4 Summary of the assessment ... 6

**2.2 Number of patients or demarcation of patient groups eligible for treatmentn ... 7**

**2.3 Requirements for a quality-assured application ... 7**

**2.4 Treatment costs ... 7**

**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 Remdesivir ... 9**

**3. Bureaucratic costs calculation ... 10**

**4. Process sequence ... 10**

## 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 online 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 16 September 2022, 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 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, sentence 7).

On 14 October 2022, the pharmaceutical company has submitted a dossier 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 "for the treatment of 2019 coronavirus disease (COVID-19) in paediatric patients (with a body weight of at least 40 kg) who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 January 2023 on the G-BA website (www.g-ba.de), 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, 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 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 and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

**Therapeutic indication of the resolution (resolution of 6 April 2023):**

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children and adolescents weighing at least 40 kg with a COVID-19 disease who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19

Appropriate comparator therapy for remdesivir:

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

- 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. In the present therapeutic indication, in addition to remdesivir, casirivimab/ imdevimab, sotrovimab and tixagevimab/ cilgavimab are approved for the treatment of children and adolescents aged 12 years and older weighing at least 40 kg with a COVID-19 disease who do not require supplemental oxygen and are at increased risk of developing a severe course of COVID-19. For the symptomatic treatment of viral infections, medicinal treatment options such as analgesics or antipyretics are also available.

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 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.

A majority of children and adolescents with mild to moderate, symptomatic COVID-19 disease can be treated as outpatients. Specific therapeutic measures are usually not required for mild to moderate, symptomatic COVID-19 disease. For subjects in outpatient care, supportive measures may include, e.g. analgesics or antipyretics and, for previously ill patients, thromboembolism prophylaxis if necessary.

The combination of active ingredients casirivimab/ imdevimab and sotrovimab were assessed by the G-BA as part of the early benefit assessment for the present therapeutic indication. For children and adolescents aged 12 years and older weighing at least 40 kg with COVID-19 disease who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19, an additional benefit of casirivimab/ imdevimab and sotrovimab has not been proven since no suitable data were available for the benefit assessment. Tixagevimab/ cilgavimab has only recently been approved in the therapeutic indication being assessed. A resolution according to Section 35a SGB V is not yet available for this active ingredient. 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, these active ingredients do not represent a component of the specific appropriate comparator therapy at this point in time.

In moderate and severe courses of COVID-19, hospitalisation may be indicated. In particular, severe organ involvement (lung, kidney) may also require intensive care intervention. For children and adolescents 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. In children and adolescents with low-flow/ high-flow oxygen therapy or non-invasive/ invasive ventilation, therapy with dexamethasone is recommended. 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. These therapies can also be used during therapy with remdesivir.

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 order.

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 remdesivir is assessed as follows:

Additional benefit is not proven for the treatment of children and adolescents weighing at least 40 kg with COVID-19 disease who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19.

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 hospitalisation or were ≥ 60 years of age were enrolled in the study. Of the 584 patients enrolled, only 8 corresponded to the sub-population to be considered here (N = 3 in the intervention arm and N = 5 in the control arm). In these 8 patients aged 12 to < 18 years and weighing at least 40 kg, no event occurred in the endpoints collected - except for a single adverse event (AE) in the control arm - (preferred term fatigue).

For the assessment of the additional benefit of remdesivir for the treatment of children and adolescents weighing at least 40 kg with a COVID-19 disease who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, the pharmaceutical company thus does not present suitable data compared to the appropriate comparator therapy.

Nor is sufficient justification provided for transferability of the adult results to children and adolescents weighing at least 40 kg. An additional benefit is therefore not proven.

### 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 as follows: “for the treatment of 2019 coronavirus disease (COVID-19) in adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19". Only children and adolescents under 18 years of age weighing at least 40 kg are considered here. The appropriate comparator therapy was determined by G-BA to be a therapy according to doctor's instructions.

The pharmaceutical company submits the results of the placebo-controlled RCT GS9012 with the dossier for the assessment of additional benefit. Of the 584 patients enrolled in the study, only 8 corresponded to the sub-population to be considered here (N = 3 in the intervention arm and N = 5 in the control arm). Due to the small sample size and the lack of occurred events in the endpoints surveyed, the data presented are unsuitable to address the questions of the

benefit assessment. Nor is sufficient justification provided for transferability of the adult results to children and adolescents weighing at least 40 kg. In the overall assessment, for children and adolescents weighing at least 40 kg with COVID-19 disease who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19, the additional benefit for remdesivir compared with the appropriate comparator therapy is 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 G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier. The derived patient numbers are subject to significant uncertainties.

## 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: 20 February 2023):

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

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 listed in the LAUER-TAXE® (last revised: 15 March 2023).

Remdesivir is listed in the LAUER-TAXE®, but is only dispensed as a clinic pack. 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-.

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 |
| Therapy according to doctor's instructions | Different from patient to patient | | | |
| Appropriate comparator therapy | | | | |
| Therapy according to doctor's instructions | Different from patient to patient | | | |

Consumption:

The (daily) doses recommended in the product information were used as the calculation basis.

| 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 | Initial dose:<br>200 mg<br><br>Maintenance dose:<br>100 mg | Initial dose:<br>200 mg<br><br>Maintenance dose:<br>100 mg | Initial dose:<br>2 x 100 mg<br><br>Maintenance dose:<br>1 x 100 mg | 3 | 4 x 100 mg |
| Therapy according to doctor's instructions | Different from patient to patient | | | | |
| 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 (clinic purchase registry) | Value added tax (19%) | Costs of the medicinal product |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Remdesivir 100 mg | 1 PIC | € 345.00 | € 65.55 | € 410.55 |
| Therapy according to doctor's instructions | Different from patient to patient | | | |
| 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 | | | | |

LAUER-TAXE® last revised: 15 March 2023

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 need 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 Remdesivir

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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 25 October 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 October 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 17 October 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 January 2023, and the written statement procedure was initiated with publication on the G-BA website on 16 January 2023. The deadline for submitting written statements was 6 February 2023.

The oral hearing was held on 20 February 2023.

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 March 2023, and the proposed resolution was approved.

At its session on 6 April 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 25 October 2022 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 15 February 2023 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 20 February 2023 | Conduct of the oral hearing |
| Working group Section 35a | 1 March 2023<br>15 March 2023<br>22 March 2023 | Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure |
| Subcommittee on Medicinal Products | 28 March 2023 | Concluding discussion of the draft resolution |
| Plenum | 6 April 2023 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 6 April 2023

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

Prof. Hecken