Remdesivir (COVID-19, with supplemental oxygen, ≥ 4 weeks to < 12 years)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
COVID-19	coronavirus disease 2019
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug remdesivir. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 October 2022.

Research question

The aim of the present report is to assess the added benefit of remdesivir in comparison with the appropriate comparator therapy (ACT) for the treatment of coronavirus disease 2019 (COVID-19) in children aged 4 weeks to 11 years and weighing at least 3 kg with pneumonia requiring supplemental oxygen (low-flow oxygen or high-flow oxygen or other non-invasive ventilation at start of treatment). The assessment of remdesivir in adults and adolescents aged 12 years and older and weighing at least 40 kg in this therapeutic indication has already been carried out (see dossier assessment A21-38, as well as the G-BA resolution and justification).

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of remdesivir

Therapeutic indication	**ACT**[a]
Children aged 4 weeks to 11 years and weighing at least 3 kg with COVID-19[b, c] and pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)	Treatment of physician's choice[d]

a. Presented is the ACT specified by the G-BA.
b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences.
c. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. so-called variants of concern [VOC]) are also taken into account when recording and interpreting the results on efficacy.
d. Depending on the severity of disease, both drug therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) should be taken into account in the treatment of physician's choice, if indicated.

COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VOC: variants of concern

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Randomized controlled trials (RCTs) are used for the derivation of added benefit.

Results

Data presented by the company – GS5823 study

Study GS5823 is a non-randomized, open-label, single-arm study that enrolled patients aged 0 days to < 18 years with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. All patients were hospitalized at the time of study inclusion and required medical care for COVID-19. The company presented data on a total of 53 patients who had received remdesivir largely in compliance with the current Summary of Product Characteristics (SPC). Of these, at least 33 patients do not correspond to the therapeutic indication under assessment due to their age and/or ventilation status.

The company argued that, on the basis of the basic comparability of the disease due to the underlying viral cause, the data on adults can be assumed to be transferable to the paediatric population. Against this background, the company assumed that the added benefit of remdesivir for adults determined by the G-BA can be transferred to the population of children in this therapeutic indication on the basis of the available study results. Overall, when considering the available evidence for the paediatric patient population, the company claimed a hint of a non-quantifiable added benefit for remdesivir in comparison with the ACT.

Assessment of the data presented by the company

The data presented by the company are unsuitable for the benefit assessment of remdesivir in comparison with the ACT.

The results from the single-arm GS5823 study alone are not suitable for the assessment of the added benefit of remdesivir in comparison with the ACT, as they do not allow a comparison with the ACT.

The evidence transfer from adults to the paediatric target population intended by the company is based solely on considerations without supporting them with data. This approach is not appropriate and an assessment of the comparability of paediatric patients with adult patients based on the information provided is not possible in the present therapeutic indication.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of remdesivir.

Table 3: Remdesivir – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children aged 4 weeks to 11 years and weighing at least 3 kg with COVID-19[b, c] and pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)	Treatment of physician's choice[d]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences.
c. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. so-called variants of concern [VOC]) are also taken into account when recording and interpreting the results on efficacy.
d. Depending on the severity of disease, both drug therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) should be taken into account in the treatment of physician's choice, if indicated.

COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VOC: variants of concern

The GBA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of the present report is to assess the added benefit of remdesivir in comparison with the ACT for the treatment of COVID-19 in children aged 4 weeks to 11 years and weighing at least 3 kg with pneumonia requiring supplemental oxygen (low-flow oxygen or high-flow oxygen or other non-invasive ventilation at start of treatment).

The assessment of remdesivir in adults and adolescents aged 12 years and older and weighing at least 40 kg in this therapeutic indication has already been carried out (see dossier assessment A21-38 [3], as well as the G-BA resolution [4] and justification [5]).

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of remdesivir

Therapeutic indication	**ACT**[a]
Children aged 4 weeks to 11 years and weighing at least 3 kg with COVID-19[b, c] and pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)	Treatment of physician's choice[d]
a. Presented is the ACT specified by the G-BA. b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences. c. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. so-called variants of concern [VOC]) are also taken into account when recording and interpreting the results on efficacy. d. Depending on the severity of disease, both drug therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) should be taken into account in the treatment of physician's choice, if indicated. COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VOC: variants of concern	

The company followed the G-BA's specification of the ACT.

In its dossier, the company also addressed the research question of children and adolescents who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. This research question is subject of benefit assessment A22-112 [6], where this part of the dossier is assessed.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

RCTs are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on remdesivir (status: 29 August 2022)
- bibliographical literature search on remdesivir (last search on 29 August 2022)
- search in trial registries/trial results databases for studies on remdesivir (last search on 29 August 2022)
- search on the G-BA website for remdesivir (last search on 29 August 2022)

To check the completeness of the study pool:

- search in trial registries for studies on remdesivir (last search on 2 November 2022), for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the direct comparison of remdesivir versus the ACT.

As the company did not identify any RCTs for direct comparisons, it presented the non-randomized single-arm GS5823 study [7,8] for completeness and transparency. The company conducted no systematic information retrieval for further investigations. In order to derive the added benefit, the company intended to transfer the added benefit determined in the A21-38 procedure (see Section I 2) from adults to the present therapeutic indication.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of remdesivir in comparison with the ACT. This is justified below.

I 3.1 Data presented by the company

Study GS5823

Study GS5823 is a non-randomized, open-label, single-arm study that enrolled patients aged 0 days to < 18 years with confirmed SARS-CoV-2 infection. All patients were hospitalized at the time of study inclusion and required medical care for COVID-19. Inclusion was based on body weight and age in a total of 8 different cohorts. The company presented data on a total of 53 patients (from cohorts 1, 2, 3, 4 and 8) who had received remdesivir largely in compliance with the current SPC [9]. In its dossier, the company presented only descriptive results (change from baseline to day 10 or end of study [day 28]) for these 53 children and adolescents for various outcomes.

Further considerations of the company on transferability

The company argued that, on the basis of the basic comparability of the disease due to the underlying viral cause, the data on adults can be assumed to be transferable to the paediatric population. It also argued that, although most children and adolescents have a mild course of COVID-19, they can also develop severe disease, which would then be expected to have a comparable course of disease in terms of mortality and morbidity as in adults. Against this background, the company assumed that the added benefit of remdesivir for adults determined by the G-BA can be transferred to the population of children in this therapeutic indication on the basis of the available study results. Overall, when considering the available evidence for the paediatric patient population, the company claimed a hint of a non-quantifiable added benefit for remdesivir in comparison with the ACT.

I 3.2 Assessment of the data presented by the company

The data presented by the company are unsuitable for the benefit assessment of remdesivir in comparison with the ACT. This is explained below.

No conclusions on added benefit are possible on the basis of the GS5823 study

The company presented the results of the single-arm GS5823 study. The results from the GS5823 study alone are not suitable for the assessment of the added benefit of remdesivir in comparison with the ACT, as they do not allow a comparison with the ACT. Besides, at least 33 of the 53 patients presented in the company's dossier do not correspond to the therapeutic indication under assessment due to their age and/or ventilation status.

The evidence transfer from adults to the paediatric target population intended by the company is based solely on considerations without supporting them with data

Under certain circumstances, results can be transferred from one population to another one for which no or only insufficient data are available. This requires, among other things, sufficient similarity of pathogenesis and clinical picture as well as data on the intervention and the comparator therapy in the therapeutic indication that support comparable effects with regard to patient-relevant outcomes between the populations.

The assessment of such similarity between adults and children in the present therapeutic indication is not possible based on the considerations of the company.

- In order to adequately discuss the possibility of transferability, it would be necessary to compare patient characteristics and results in adults with those in children. The company did not provide an analysis of the comparability of the adult patients included in the available studies with regard to patient characteristics and the results with the paediatric target population of study GS5823 for the present benefit assessment.

- Rather, there is a lack of systematic processing of the evidence on children in the present therapeutic indication. The company provided no information retrieval on further investigations, neither for the ACT nor for the intervention arm.
- The question of whether the course of COVID-19 in the paediatric target population is comparable to the one in adults in terms of mortality and morbidity was not addressed by literature references or other data.
- For adolescents, no added benefit was derived already in procedure A21-38 (see dossier assessment A21-38 [3], G-BA resolution [4] and justification [5]) because a transferability of the results was not assumed.

Conclusion

The results presented by the company are unsuitable for the assessment of the added benefit of remdesivir in comparison with the ACT. On the one hand, the results from the single-arm GS5823 study alone are not suitable for the benefit assessment, as they do not allow a comparison with the ACT. On the other, the evidence transfer from adults to the paediatric target population intended by the company is based solely on considerations without supporting them with data. This approach is not appropriate and an assessment of the comparability of paediatric patients with adult patients in the present therapeutic indication is not possible based on the information provided.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of remdesivir in comparison with the ACT in children aged 4 weeks to 11 years and weighing at least 3 kg with COVID-19 and pneumonia requiring supplemental oxygen. There is no hint of an added benefit of remdesivir in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of remdesivir in comparison with the ACT.

Table 5: Remdesivir – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Children aged 4 weeks to 11 years and weighing at least 3 kg with COVID-19[b, c] and pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)	Treatment of physician's choice[d]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In case of a positive rapid antigen test, the diagnosis of SARS-CoV-2 infection should be confirmed by a PCR test, especially if the results have therapeutic consequences.
c. It is recommended that relevant SARS-CoV-2 mutation variants (e.g. so-called variants of concern [VOC]) are also taken into account when recording and interpreting the results on efficacy.
d. Depending on the severity of disease, both drug therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-drug therapies (e.g. oxygen support, type of ventilation, balanced fluid therapy) should be taken into account in the treatment of physician's choice, if indicated.

COVID-19: coronavirus disease 2019; G-BA: Federal Joint Committee; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VOC: variants of concern

The assessment described above deviates from that by the company, which derived a hint of a non-quantifiable added benefit for paediatric patients in the present therapeutic indication.

The GBA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Remdesivir (COVID-19) – Nutzenbewertung gemäß § 35a SGB V [online]. 2021 [Accessed: 24.11.2022]. URL: https://www.iqwig.de/download/a21-38_remdesivir_nutzenbewertung-35a-sgb-v_v1-0.pdf.

4. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie Anlage XII –Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Remdesivir (COVID-19, ≥ 12 Jahre, Erfordernis zusätzlicher Sauerstoffzufuhr); Vom 16. September 2021 [online]. 2021 [Accessed: 24.11.2022]. URL: https://www.g-ba.de/downloads/39-261-5021/2021-09-16_AM-RL-XII_Remdesivir_D-665_BAnz.pdf.

5. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Remdesivir (COVID-19, ≥ 12 Jahre, Erfordernis zusätzlicher Sauerstoffzufuhr); Vom 16. September 2021 [online]. 2021 [Accessed: 24.11.2022]. URL: https://www.g-ba.de/downloads/40-268-7846/2021-09-16_AM-RL-XII_Remdesivir_D-665_TrG.pdf.

6. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Remdesivir (COVID-19, ohne zusätzliche Sauerstoffzufuhr, erhöhtes Risiko für schweren Verlauf, < 18 Jahre) – Nutzenbewertung gemäß § 35a SGB V [online]. URL: Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/888/.

7. Gilead Sciences. Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN) [online]. 2020 [Accessed: 28.11.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT04431453.

8. Gilead Sciences. A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734) in Participants from Birth to < 18 Years of Age with COVID-19 [online]. 2020 [Accessed: 28.11.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=GS-US-540-5823.

9. Gilead Sciences Ireland. Fachinformation Veklury (Remdesivir) 100 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung. Stand der Information: September. 2022.

The full report (German version) is published under https://www.iqwig.de/en/projects/a22-113.html.