Remdesivir (COVID-19, without supplemental oxygen, increased risk for severe disease, < 18 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 and adolescents weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The assessment of remdesivir in adult patients in this therapeutic indication has already been carried out (see dossier assessment A22-04, 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 and adolescents weighing at least 40 kg with COVID-19[b, c] who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID19	Treatment of physician's choice[d, e]

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. Recently, the intravenous drugs casirivimab/imdevimab, sotrovimab and tixagevimab/cilgavimab have been approved for the treatment of COVID-19 patients aged 12 years and older who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time.
e. 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 – GS9012 study

The GS9012 study is a placebo-controlled, double-blind, randomized phase 3 study on the outpatient treatment with remdesivir in patients with early-stage COVID-19. The study included symptomatic patients aged 12 years and older and weighing ≥ 40 kg with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. At the time of study inclusion, additional oxygen supply was not allowed to be necessary or expected for the included patients. Furthermore, COVID-19 patients had to have at least one pre-existing risk factor for disease progression up to hospitalization.

The subpopulation of the RCT GS9012 relevant for the present benefit assessment comprises 8 patients aged 12 to < 18 years and weighing at least 40 kg (n = 3 in the intervention arm and n = 5 in the control arm). Remdesivir was administered in compliance with the current Summary of Product Characteristics (SPC).

The company argued that, although only few paediatric patients were included in the GS9012 study, the data on adults can be assumed to be transferable to the paediatric population on the basis of the basic comparability of the disease due to the underlying viral cause. 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 and adolescents 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 RCT GS9012 is in principle suitable for a comparison of remdesivir with the ACT. However, in the present therapeutic indication, only 8 patients were included in the GS9012 study and no events were observed for the outcomes presented, except for a single adverse event (AE) (Preferred Term fatigue) in the control arm. Thus, the data basis is insufficient to assess the added benefit.

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.

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 and adolescents weighing at least 40 kg with COVID-19[b, c] who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID19	Treatment of physician's choice[d, e]	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. Recently, the intravenous drugs casirivimab/imdevimab, sotrovimab and tixagevimab/cilgavimab have been approved for the treatment of COVID-19 patients aged 12 years and older who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time.
e. 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 and adolescents weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

The assessment of remdesivir in adult patients in this therapeutic indication has already been carried out (see dossier assessment A22-04 [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 and adolescents weighing at least 40 kg with COVID-19[b, c] who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID19	Treatment of physician's choice[d, e]

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. Recently, the intravenous drugs casirivimab/imdevimab, sotrovimab and tixagevimab/cilgavimab have been approved for the treatment of COVID-19 patients aged 12 years and older who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time.
e. 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 with COVID-19 and pneumonia who require supplemental oxygen. This research question is subject of benefit assessment A22-113 [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 lists 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

No relevant study was identified from the check.

Neither the data presented by the company on the RCT GS9012 [7-9] nor the transfer of the added benefit determined for adults in the A22-04 procedure (see Section I 2) to the present therapeutic indication are suitable for deriving 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 GS9012

The GS9012 study is a placebo-controlled, double-blind, randomized phase 3 study on the outpatient treatment with remdesivir in patients with early-stage COVID-19. The study included symptomatic patients aged 12 years and older and weighing ≥ 40 kg with confirmed SARS-CoV-2 infection. At the time of study inclusion, additional oxygen supply was not allowed to be necessary or expected for the included patients. Furthermore, COVID-19 patients had to have at least one pre-existing risk factor for disease progression up to hospitalization. Study GS9012 was completed in May 2021 and already described in detail in dossier assessment A22-04 [3].

The subpopulation of the RCT GS9012 relevant for the present research question comprises 8 patients aged 12 to < 18 years and weighing at least 40 kg (n = 3 in the intervention arm and n = 5 in the control arm). Remdesivir was administered in compliance with the current SPC [10].

In its dossier, the company presented results for various outcomes for this subpopulation (see I Appendix B of the full dossier assessment). No events occurred in either treatment arm for any of the outcomes, except for a single AE (Preferred Term fatigue) in the control arm.

Further considerations of the company on transferability

The company argued that, although only few paediatric patients were included in the GS9012 study, the data on adults can be assumed to be transferable to the paediatric population on the basis of the basic comparability of the disease due to the underlying viral cause. 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 and adolescents 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 GS9012 study

The RCT GS9012 is in principle suitable for a comparison of remdesivir with the ACT (see also dossier assessment A22-04 [3]). However, in the present therapeutic indication, only 8 patients were included in the GS9012 study and no events were observed for the outcomes presented, except for a single AE (Preferred Term fatigue) in the control arm (see supplementary presentation in I Appendix B of the full dossier assessment). Thus, the data basis is insufficient to assess the added benefit.

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 and adolescents in the present therapeutic indication is not possible based on the considerations of the company.

- In the RCT GS9012, only 3 patients in the present therapeutic indication received remdesivir. Sufficient similarity between the populations in terms of patient characteristics and patient-relevant outcomes cannot be assessed on the basis of so few patients.
- 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 and adolescents (especially with regard to the number and/or type of risk factors and age groups). The company did not analyse this on the basis of paediatric patients who may have been included in other studies and the adults in study GS9012. The company did not provide an information retrieval on further investigations for the ACT or for the intervention arm.
- There is no literature search conducted by the company to determine whether the risk factors for severe disease are identical between adults, adolescents and children. The question of whether the course of COVID-19 in the paediatric target population at increased risk of progressing to severe COVID-19 is comparable to the one in adults in terms of mortality and morbidity was not addressed by literature references or other data.

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 data presented by the company cannot be meaningfully interpreted, as only 8 patients in the present therapeutic indication were included and no events were observed for patient-relevant outcomes. 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 to assess the added benefit of remdesivir in comparison with the ACT in children and adolescents weighing at least 40 kg with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. 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 and adolescents weighing at least 40 kg with COVID-19[b, c] who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID19	Treatment of physician's choice[d, e]	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. Recently, the intravenous drugs casirivimab/imdevimab, sotrovimab and tixagevimab/cilgavimab have been approved for the treatment of COVID-19 patients aged 12 years and older who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The clinical significance of these therapy options cannot be assessed at the present time.
e. 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.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-112.html.