Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Remdesivir (COVID-19, ≥ 12 years, requiring supplemental oxygen)

of 16 September 2021

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient remdesivir (Veklury) has been on the market in Germany since May 2020 due to pandemic-related exemptions (Arzneimittelgesetz-Zivilschutzausnahmeverordnung (Medicines Act - Civil Protection Exception Ordinance); Section 26b Krankenhausfinanzierungsgesetz (KHG)(Hospital Financing Act)). Remdesivir received conditional approval on 3 July 2020 for the treatment of COVID-19 in adults and adolescents with pneumonia requiring supplemental oxygen.

Due to minor sales turnover, the active ingredient remdesivir was initially exempted from the benefit assessment and the pharmaceutical company's obligation to submit evidence according to Chapter 5, Section 5 VerfO by resolution of 20 August 2020. By a new resolution of 3 December 2020, the exemption was limited until 31 March 2021, and the pharmaceutical company was accordingly requested to submit evidence in accordance with Chapter 5, Section 5, paragraphs 1 to 6 VerfO, within three months. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Chapter 5, Section 15, paragraph 4, sentence 1, in conjunction with Section 8, paragraph 1, number 6 VerfO, on 1 April 2021.

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 1 July 2021, thus initiating the written statement procedure. In addition, an oral hearing was also 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 and in adolescents (aged 12 to less than 18 years and weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)

Therapeutic indication of the resolution (resolution from 16.09.2021):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) COVID-19 infected adults with pneumonia requiring supplemental oxygen who receive low-flow oxygen at start of treatment

Appropriate comparator therapy:

Therapy according to doctor's instructions

b) COVID-19 infected adults with pneumonia requiring supplemental oxygen who receive high-flow oxygen or non-invasive ventilation at start of treatment

Appropriate comparator therapy:

Therapy according to doctor's instructions

1 General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

c) Adolescents with COVID-19 who have pneumonia requiring supplemental oxygen and are receiving low-flow or high-flow oxygen or non-invasive ventilation at start of treatment

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 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 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 Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. Comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally accepted state of medical knowledge.

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

on 1. In the therapeutic indication for the treatment of COVID-19 in adults and adolescents, the active ingredient dexamethasone is approved in addition to remdesivir for infections requiring supplemental oxygen.

on 2. A non-medicinal treatment is unsuitable as a comparator therapy in this therapeutic indication.

on 3. In the present therapeutic indication, there are no resolutions and guidelines of the G-BA.

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication.

At present, the treatment of COVID-19 disease is based on the clinical expression (mild, severe) with the predominant symptoms.

A predominant percentage of patients with COVID-19 disease can be managed on an outpatient basis (i.e., in-home isolation). For these patients in outpatient care, supportive measures may include analgesics or antipyretics.

For moderate and severe courses, inpatient treatment may be indicated. In particular, severe organ involvement (lung, kidney) may also require intensive care intervention. For patients in inpatient care with more severe courses, 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. Therapy with dexamethasone should be implemented in patients with severe (SpO2 < 90 %, respiration rate >30/min) or critical (ARDS, sepsis, ventilation, vasopressor administration) COVID-19 disease[2].

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.

Depending on the severity of the disease, both medicinal therapies (e.g. analgesics, antipyretics, dexamethasone, anticoagulation/thrombosis prophylaxis, antibiotics) and non-medicinal therapies (e.g. oxygen administration, type of ventilation, balanced fluid therapy) are to be taken into account in the therapy based on doctor's instructions.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2 S3 Guideline - Recommendations for the inpatient treatment of patients with COVID-19 https://www.awmf.org/uploads/tx_szleitlinien/113-001LGl_S3_Empfehlungen-zur-stationaeren-Therapie-von-Patienten-mit-COVID-19__2021-05.pdf (last accessed: 30 August 2021)

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of remdesivir is assessed as follows:

a) COVID-19 infected adults with pneumonia requiring supplemental oxygen who receive low-flow oxygen at start of treatment

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of remdesivir compared to the appropriate comparator therapy:

Hint for a minor additional benefit

b) COVID-19 infected adults with pneumonia requiring supplemental oxygen who receive high-flow oxygen or non-invasive ventilation at start of treatment

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of remdesivir compared to the appropriate comparator therapy:

An additional benefit is not proven.

c) COVID-19 infected adolescents with pneumonia requiring supplemental oxygen who receive low-flow or high-flow oxygen or non-invasive ventilation at start of treatment

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of remdesivir compared to the appropriate comparator therapy:

An additional benefit is not proven.

Justification:

The benefit assessment is based on the results of the ACTT-1, CAP-2 and GS5774-A studies. The results are evaluated separately according to ventilation status (low-flow oxygen [LFO] vs high-flow oxygen / non-invasive ventilation [HFO/NIV]) because the patient groups differ significantly concerning the severity of the disease and therefore also with regard to the importance of the treatment option dexamethasone. The recommendations for the use of dexamethasone, the only approved medicinal product currently recommended in the guidelines for the treatment of COVID-19, are based on the results of the RECOVERY study[3], which showed an effect of dexamethasone on mortality depending on the severity of COVID disease. Based on the RECOVERY study results, all patients covered by the marketing authorisation of remdesivir would benefit from treatment with dexamethasone. Invasively

3 Horby P, Lim WS, Emberson JR et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021; 384(8): 693-704. https://dx.doi.org/10.1056/NEJMoa2021436

ventilated patients benefited more than non-invasively ventilated patients requiring oxygen. In contrast, for COVID-19 patients without oxygen requirements, there was no statistically significant advantage of dexamethasone on mortality. No analyses are available for the LFO vs HFO / NIV subgroups within the patient population with oxygen demand. The extent to which the efficacy of dexamethasone depends on the severity of COVID-19 disease remains unclear but seems plausible. Thus, there is uncertainty as to the extent to which patients with LFO oxygen therapy already benefit from treatment with dexamethasone. The pharmaceutical company also uses the SOLIDARITY study, whose data, however, are not suitable for the question of the benefit assessment without further differentiated processing and separated evaluation according to ventilation status.

The ACTT-1 study is a placebo-controlled, double-blind, multicentre, multinational, randomised, parallel-group study of remdesivir conducted in 60 centres in 10 countries (Denmark, Germany, Greece, Japan, Mexico, Singapore, South Korea, Spain, United Kingdom, United States). The study included hospitalised adults with confirmed COVID-19 disease with defined minimal disease severity. A total of 1,062 patients were included and assigned in a 1:1 ratio to treatment with remdesivir (N = 541) or to the placebo group (N = 521). Remdesivir was administered for 10 days in the ACTT-1 study, compliant with marketing authorisation. In addition, patients in both arms received standard COVID-19 therapy according to local guidelines at the time.

The CAP-2 study is a placebo-controlled, double-blind, randomised, parallel-group study of remdesivir conducted exclusively in 10 centres in Wuhan, China. The study included hospitalised adults with confirmed COVID-19 disease and pneumonia. In addition, patients had to have an oxygen saturation of ≤ 94% (arterial oxygen saturation [SaO2] or SpO2) or an oxygenation index (quotient of partial pressure of oxygen [paO2] and inspiratory oxygen concentration [FiO2]) of < 300 mmHg at hospitalisation. A total of 237 patients were included and assigned in a 2:1 ratio to treatment with remdesivir (N = 158) or to the placebo group (N = 79). Remdesivir was administered for 10 days in the CAP-2 study, compliant with marketing authorisation. In addition, patients in both arms received standard COVID-19 therapy. The study was terminated before reaching the planned number of cases (n = 453) due to a decline in new cases.

Study GS5774-A is a 3-arm, open-label, multicentre, randomised, parallel-group study in which patients were treated with remdesivir for either 5 days or 10 days or received exclusively standard COVID-19 therapy. The study was conducted in 105 centres in 12 countries (Germany, France, Hong Kong, Italy, Netherlands, Switzerland, Singapore, Spain, South Korea, Taiwan, USA, United Kingdom). The study included COVID-19 infected adults with SpO2 > 94% on room air and radiological evidence of pulmonary infiltration. Patients were not allowed to be mechanically ventilated. Remdesivir was administered for 5 or up to 10 days in the GS5774-A study, compliant with the marketing authorisation. As the marketing authorisation of remdesivir covers both periods, the two study arms are described and analysed together where possible. In addition, patients in all study arms received standard COVID-19 therapy. A total of 596 patients were included and randomised in a 1:1:1 ratio to treatment with remdesivir for 5 days (N = 199), treatment with remdesivir for 10 days (N = 197), or standard therapy (N = 200) without stratification.

Due to the marketing authorisation of remdesivir, only patients with supplemental oxygen requirements at the start of the study (LFO or HFO / NIV at the start of treatment) are included for the benefit assessment. For each of the ACTT-1 and GS5774-A studies, analyses are available for the relevant sub-population, representing 59% and 16% of the total population, respectively. No separate analyses are available for the CAP-2 study. However, the population of those with supplementary oxygen requirements (without invasive ventilation) at the start

of the study accounts for 98% of the total population, which can be used for the benefit assessment.

For the CAP-2 study, there are no subgroup evaluations separated by ventilatory status, but the sub-population of patients with LFO makes up 83% of the total population, so the total population is used for the sub-population of LFO.

In all three studies, patients in the comparator arm were treated with standard therapy for COVID-19. This was defined differently in the study protocols, and only very limited information on the implementation of the appropriate comparator therapy is generally provided in the dossier. From the available documentation, it appears that dexamethasone or other corticosteroids were administered in all three studies, but to varying degrees. However, this information is only available for the respective total populations and not for the sub-populations relevant to the assessment. This further complicates the assessment of whether adequate treatment with dexamethasone occurred in these sub-populations. According to the current evidence base and the health care context, it is assumed that the administration of dexamethasone is indicated in the hyperinflammatory phase of infection in patients dependent on oxygen therapy.

Based on the available information, it is not possible to conclusively assess the extent to which the currently applicable standard of care, in particular concerning the use of dexamethasone, is implemented in the studies for less severely affected patients with LFO oxygen therapy. Thus, there are uncertainties regarding the implementation of the appropriate comparator therapy for the present studies. The studies are nevertheless used for the benefit assessment.

In contrast, dexamethasone is an essential therapy component for patients who are dependent on HFO oxygen therapy and are therefore usually in a later, more severe phase of the disease. The implementation of the appropriate comparator therapy in the studies is thus associated with considerable uncertainties. The results of the studies are nevertheless presented but not used for the benefit assessment.

The SOLIDARITY study is a randomised, open-label, parallel-group study conducted by the World Health Organization (WHO) to identify effective COVID-19 therapeutics. The study includes hospitalised adults with COVID-19 disease. However, the study is not suitable for the question of the benefit assessment without further differentiated processing of the data, as there are no evaluations separated according to ventilation status (LFO vs HFO / NIV). However, such evaluations are necessary for the present assessment. The SOLIDARITY study was conducted in 405 centres in 30 different countries. These include study centres in Egypt, Honduras, India, Indonesia, Lebanon, Pakistan, Peru and the Philippines. Medical care comparable to that available in Germany (e.g. concerning ventilation and intensive care capacities) is not generally guaranteed in these countries, making the transferability of the study results even more difficult. In summary, the SOLIDARITY study is not used for the benefit assessment of remdesivir.

Extent and probability of the additional benefit

The evaluation is based on quantitative meta-analytic summaries of the study results. A qualitative summary is performed if a quantitative summary is not appropriate for an endpoint because of the small number of studies or the presence of heterogeneity.

a) COVID-19 infected adults with pneumonia requiring supplemental oxygen who receive low-flow oxygen at start of treatment

Mortality

For the LFO sub-population, the meta-analysis showed a statistically significant difference to the benefit of remdesivir + standard therapy for the endpoint overall mortality for the studies with high certainty of results (ACTT-1 and GS5774-A). In contrast, the CAP-2 study did not show any benefits for remdesivir on overall survival that would provide a hint for an additional benefit. Therefore, the addition of the CAP-2 study leads to a heterogeneous data situation, which cannot be assessed taking into account the uncertainties regarding the implementation of the appropriate comparator therapy in the individual study populations. The mortality data can therefore not be used for the benefit assessment.

Morbidity

The endpoint recovery was assessed in all three relevant studies using different but largely congruent ordinal scales on the clinical status of the patients.
For the benefit assessment, the percentages of patients with recovery both at day 14 (CAP-2 and GS5774-A) and day 15 (ACTT-1) and at the end of the study (day 28 [CAP-2 and GS5774-A] and day 29 [ACTT-1]) are used.
For the sub-population LFO, a statistically significant difference to the advantage of remdesivir + standard therapy is shown for the endpoint recovery at day 14 / 15 in the meta-analysis for the studies with high certainty of results. The addition of the CAP-2 study with moderate certainty of results yields a statistically non-significant result with homogeneous data.
For the sub-population LFO, a statistically significant difference to the advantage of remdesivir + standard therapy is shown for the endpoint recovery at the end of the study in the meta-analysis for the studies with high certainty of results. With the addition of the CAP-2 study, the meta-analysis of all three studies also shows a statistically significant difference between the treatment groups to the benefit of remdesivir + standard therapy with homogeneous data, but with a wider confidence interval (RR 1.17; 95% CI 1.01 - 1.36). In summary, considering the uncertainties regarding the implementation of the appropriate comparator therapy in the individual study populations, a benefit for remdesivir is derived.

Quality of life

Endpoints on health-related quality of life were not collected in the included studies.

Side effects

When collecting data on SAEs and discontinuations due to AEs, disease-related events were included to a large extent in the studies. Accordingly, the results of individual frequent AEs (e.g. respiratory insufficiency) show comparable advantages for remdesivir as the results for morbidity. As a result, the overall rates of SAEs and discontinuations due to AEs are not useful for evaluating the side effects of remdesivir. However, based on the results on frequent SAEs and discontinuations due to AEs, no adverse effects of remdesivir are expected to the degree that could question the additional benefit of remdesivir.

Overall assessment

For evaluating the additional benefit of remdesivir over treatment by doctor's instructions in adults with COVID-19 disease with LFO at start of treatment, mortality (overall survival) and morbidity (recovery) results are available from the meta-analytic summary of the ACTT-1, GS5774-A, and CAP-2 studies.
In the endpoint category mortality, the available results for the endpoint overall survival show a statistically significant advantage for remdesivir compared to the appropriate comparator therapy. However, the addition of the CAP-2 study leads to a heterogeneous data situation so that no conclusions can be drawn for the benefit assessment.

For the endpoint category morbidity, advantages are also shown for remdesivir concerning the endpoint recovery. However, the addition of the CAP-2 study in the evaluation on day 14/15 leads to a statistically non-significant result. When the CAP-2 study is added to the end-of-study recovery evaluation, the advantage for remdesivir remains statistically significant but with a wider confidence interval.
No data are available on health-related quality of life, as health-related quality of life was not assessed in the studies.
The overall rates of SAEs and discontinuations due to AEs for the evaluation of side effects of remdesivir are not usable due to the extensive co-recording of disease-related events.
Uncertainties relate to the implementation of the appropriate comparator therapy in the included studies. Although the standard therapy against COVID-19 used in the studies also contained corticosteroids, these were used to a very different extent in the studies. According to the S3 Guideline - Recommendations for the inpatient treatment of patients with COVID-19 - treatment with dexamethasone should be given to patients with severe (SpO2 < 90 %, respiratory rate > 30/min) or critical (ARDS, sepsis, ventilation, vasopressor administration) COVID-19 disease. It is unclear how and to what extent this recommendation also applies to patients with moderate severity COVID-19 disease treated with LFO. According to the clinical assessment experts, in the treatment phase of COVID-19 with LFO, simultaneous use of remdesivir and dexamethasone is only considered in a short transition phase from the virus replication to the hyperinflammatory phase of the disease. It is also unclear whether the use of dexamethasone in the studies during this transitional phase was of sufficient magnitude.
Overall, remdesivir showed positive effects compared to standard therapy concerning endpoint recovery. Uncertainties arise in implementing the appropriate comparator therapy and due to the heterogeneous study situation in the endpoint category mortality.
Taken together, a minor additional benefit is identified for remdesivir compared to the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

In general, it can be assumed that the treatment of hospitalised patients with COVID-19 has improved since the beginning of the pandemic. Therefore, the treatment of COVID-19 in the included studies conducted at the beginning of the pandemic can be transferred to the current medical treatment situation only to a limited extent. As the data on side effects cannot be assessed, additional uncertainties arise. Finally, the transferability of the results in the endpoint recovery to the German health care context is also associated with uncertainties since an essential component of the endpoint is discharge from the hospital, which is regularly subject to regional differences in multicentre studies.
Due to the limitations of the available evidence, a hint for a minor additional benefit can be derived despite the availability of several RCTs about the reliability of data.

b) COVID-19 infected adults with pneumonia requiring supplemental oxygen who receive high-flow oxygen or non-invasive ventilation at start of treatment

There is considerable uncertainty in all studies concerning implementing the appropriate comparator therapy in patient population b). According to the S3 Guideline - Recommendations for the inpatient treatment of patients with COVID-19 - treatment with dexamethasone should be given to patients with severe (SpO2 < 90 %, respiratory rate > 30/min) or critical (ARDS, sepsis, ventilation, vasopressor administration) COVID-19 disease. According to the generally accepted state of medical knowledge, dexamethasone is therefore an essential part of the therapy for the usually more severely affected patients who receive HFO oxygen therapy. From the data on the use of dexamethasone, which is only available for the total population, it is impossible to infer beyond doubt the percentage of patients in the

sub-populations relevant to the evaluation who were treated with dexamethasone. With respect to the current standard of care, it can be assumed that a higher percentage of patients receiving HFO oxygen would receive dexamethasone, particularly compared to the ATCC-1 and GS5774-A studies.
The results of the studies are nevertheless presented but not used for the benefit assessment.

Mortality

For the sub-population, HFO / NIV, the meta-analysis for the studies with high certainty of results showed no statistically significant difference between the treatment groups for the endpoint overall mortality.

Morbidity

For the sub-population HFO / NIV, the meta-analysis for the studies with high certainty of results showed no statistically significant difference between the treatment groups for the endpoint recovery, both at day 14 / 15 and at the end of the study.

Quality of life

Endpoints on health-related quality of life were not collected in the included studies.

Side effects

When collecting data on SAEs and discontinuations due to AEs, disease-related events were included to a large extent in the studies. Accordingly, the results of individual frequent AEs (e.g. respiratory insufficiency) show comparable advantages for remdesivir as the results for morbidity. As a result, the overall rates of SAEs and discontinuations due to AEs are not useful for evaluating the side effects of remdesivir.

Overall assessment

For the evaluation of the additional benefit of remdesivir compared to treatment according to doctor's instructions in adults with COVID-19 disease with HFO / NIV at the start of treatment, mortality (overall survival) and morbidity (recovery) results are available from the meta-analytic summary of the ACTT-1 and GS5774-A studies.
There is considerable uncertainty in all studies in implementing the appropriate comparator therapy in patients with HFO / NIV at the start of treatment. The study results are nevertheless presented but not used for the benefit assessment.
For the endpoint overall mortality no statistically significant difference was detected between the treatment groups.
There was also no statistically significant difference between the treatment groups for the morbidity endpoint recovery both at day 14 / 15 and at the end of the study.
Endpoints on health-related quality of life were not collected in the included studies.
The overall rates of SAEs and discontinuations due to AEs for evaluating side effects of remdesivir are not usable due to the extensive co-recording of disease-related events.
Regardless of the uncertainties in the extent to which the appropriate comparator therapy can be considered to be fully implemented, there would be neither positive nor negative effects for remdesivir in adults receiving HFO / NIV at the start of treatment, even when assessed in terms of content.
In summary, for COVID-19 infected adults with pneumonia requiring HFO / NIV at the start of treatment, there is no hint of an additional benefit of remdesivir compared to the appropriate comparator therapy. Thus, an additional benefit is not proven.

c) Adolescents with COVID-19 who have pneumonia requiring supplemental oxygen and are receiving low-flow or high-flow oxygen or non-invasive ventilation at start of treatment

No adolescents were included in the studies in the sub-populations relevant for the benefit assessment. Furthermore, the pharmaceutical company does not present any data on the transfer of the results to adolescents. As there are clearly different mortality risks for COVID-19 depending on age, the results of the benefit assessment observed for adults cannot be transferred to adolescents. Therefore, there are no usable data for adolescents and an additional benefit is not proven for this patient population either.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Veklury with active ingredient remdesivir.

Remdesivir is approved for the treatment of coronavirus disease 2019 (COVID-19) in adults and in adolescents (aged 12 to less than 18 years and weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment).

In the therapeutic indication to be considered, 3 patient groups were distinguished:

a) COVID-19 infected adults with pneumonia requiring supplemental oxygen who receive low-flow oxygen at start of treatment

b) COVID-19 infected adults with pneumonia requiring supplemental oxygen who receive high-flow oxygen or non-invasive ventilation at start of treatment

c) Adolescents with COVID-19 who have pneumonia requiring supplemental oxygen and are receiving low-flow or high-flow oxygen or non-invasive ventilation at start of treatment

According to doctor's instructions, the appropriate comparator therapy for all three patient groups was determined to be therapy.

About patient group a)

For this patient group, mortality (overall survival) and morbidity (recovery) results are available from the meta-analytic summary of the ACTT-1, GS5774-A, and CAP-2 studies.
In the endpoint category mortality, the available results for the endpoint overall survival show a heterogeneous data situation for remdesivir compared to the appropriate comparator therapy. The results in the endpoint mortality are therefore not assessable overall. For the endpoint category morbidity, advantages are shown for remdesivir concerning the endpoint recovery. No data are available on health-related quality of life. The overall rates of SAEs and discontinuations due to AEs for evaluating side effects of remdesivir are not usable.
Uncertainties relate to the implementation of the appropriate comparator therapy in the included studies. Although the standard therapy against COVID-19 used in the studies also contained corticosteroids, these were used to a very different extent in the studies. Treatment with dexamethasone should be given to patients with severe or critical COVID-19 disease. It is unclear whether dexamethasone was used to a sufficient extent in the studies.
Overall, remdesivir showed positive effects compared to standard therapy with respect to the endpoint recovery. Uncertainties arise in the implementation of the appropriate comparator therapy, non-assessable data on side effects and due to the heterogeneous study situation in the endpoint category mortality.

In general, the treatment of COVID-19 in the included studies conducted at the beginning of the pandemic can only be transferred to the current medical treatment situation to a limited extent.
Taken together, a hint for a minor additional benefit is identified for remdesivir compared with the appropriate comparator therapy.

About patient group b)

For this patient group, mortality (overall survival) and morbidity (recovery) results are available from the meta-analytic summary of the ACTT-1 and GS5774-A studies.
There are major uncertainties in the implementation of the appropriate comparator therapy with regard to the adequate use of dexamethasone. The study results are nevertheless presented but not used for the benefit assessment.
For the endpoint overall mortality no statistically significant difference was detected between the treatment groups.
There was also no statistically significant difference between the treatment groups for the morbidity endpoint recovery both at day 14 / 15 and at the end of the study.
Endpoints on health-related quality of life were not collected in the included studies.
The overall rates of SAEs and discontinuations due to AEs for evaluating side effects of remdesivir are not usable due to the extensive co-recording of disease-related events.
Regardless of the uncertainties in the extent to which the appropriate comparator therapy can be considered to have been fully implemented, even if the overall results were evaluated in terms of content, there would be neither positive nor negative effects for remdesivir.
In summary, for COVID-19 infected adults with pneumonia requiring HFO / NIV at the start of treatment, there is no hint of an additional benefit of remdesivir compared to the appropriate comparator therapy. Thus an additional benefit is not proven.

About patient group c)

No adolescents were included in the studies in the sub-populations relevant for the benefit assessment. Furthermore, the pharmaceutical company does not present any data on the transfer of the results to adolescents. As there are clearly different mortality risks for COVID-19 depending on age, the results of the benefit assessment observed for adults cannot be transferred to adolescents. Therefore, there are no usable data for adolescents and an additional benefit is not proven for this patient population either.

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 (commission A21-38). The infection figures reported to the RKI from the situation reports as of 23 March 2021 are used as the basis.

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 the general incidence of infection, population protection measures adopted or withdrawn in the future, the progress of population vaccination coverage, and the spread and influence of further variants of SARS-CoV-2.

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: 8 September 2021):

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

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

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.

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 package plus 19 % value-added tax, in deviation from the LAUER-TAXE® data usually taken into account. In Module 3, the company specifies a hospital pharmacy purchase price of € 460.00 excluding value-added tax.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Remdesivir	1 x daily	1	5 – 10	5 - 10
Appropriate comparator therapy				
Therapy according to doctor's instructions	Patient-individual			

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	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	5 - 10	6 x 100 mg – 11 x 100 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions	Patient-individual				

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (delivery price of the pU)	Value-added tax	Costs after deduction of statutory rebates
Medicinal product to be assessed				
Remdesivir	1 PIC	€ 460	€ 87.40	€ 547.40
Appropriate comparator therapy				
Therapy according to doctor's instructions	Patient-individual			
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 considered 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 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 11 August 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 1 April 2021, 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 1, sentence 2 VerfO.

By letter dated 1 April 2021 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 1 April 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 July 2021. The deadline for submitting written statements was 22 July 2021.

The oral hearing was held on 10 August 2021.

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 the 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 26 July 2021, and the proposed resolution was approved.

At its session on 16 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Sub-committee Medicinal product	11 August 2020	Determination of the appropriate comparator therapy
Working group Section 35a	26 July 2021	Information on statements received; preparation of the oral hearing
Sub-committee Medicinal product	10 August 2021	Conduct of the oral hearing,
Working group Section 35a	17 August 2021 31 August 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Sub-committee Medicinal product	7 September 2021	Final discussion of the draft resolution
Plenum	16 September 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 September 2021

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

Prof. Hecken