Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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 (COVID-19, ≥ 12 years, requiring supplemental oxygen)

of 16 September 2021

At its session on 16 September 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No 49a of 31 March 2009), as last amended by the publication of the resolution of TT. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient remdesivir as follows:

Remdesivir

Resolution of: 16 September 2021
Entry into force on: 16 September 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 3 July 2020):

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 of 16 September 2021):

see therapeutic indication according to marketing authorisation

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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.

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	↑	Advantage in endpoint recovery
Health-related quality of life	∅	No data provided on quality of life
Side effects	n.a.	There are no assessable data.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔ : no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-38) unless otherwise indicated.

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	∅	No data provided on quality of life
Side effects	n.a.	There are no assessable data.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔ : no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	∅	No data provided on quality of life
Side effects	n.a.	There are no assessable data.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔ : no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

Meta-analytic summary of the ACTT-1, CAP-2 and GS5774-A studies divided into the sub-populations of adult patients with low-flow oxygen (LFO) at start of treatment and adult patients with high-flow oxygen (HFO) or non-invasive ventilation (NIV) at start of treatment relevant for the evaluation

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

Mortality

Endpoint Sub-population Study	**Remdesivir + standard therapy**		**Placebo[a] + standard therapy**		**Remdesivir + standard therapy vs placebo[a] + standard therapy**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
Overall mortality (end of study)					
Patients with LFO at start of treatment					
Studies with high certainty of results					
ACTT-1	232	9 (3.9)	203	25 (12.3)	0.32 [0.15; 0.66]; 0.001
GS5774-A[c]	52	0 (0)	36	4 (11.1)	0.08 [< 0.01; 1.40]; 0.016
Total[d]					0.28 [0.14; 0.56]; < 0.001
+ study with moderate certainty of results[g]					
CAP-2	158	22 (13.9)	78	10 (12.8)	1.09 [0.54; 2.18]; 0.870
Total (all 3 studies)				Significant heterogeneity:	p = 0.021

Morbidity

Endpoint Sub-population Study	Remdesivir + standard therapy		Placebo[a] + standard therapy		Remdesivir + standard therapy vs placebo[a] + standard therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
Recovery to day 14 / 15					
Patients with LFO at start of treatment					
Studies with high certainty of results					
ACTT-1	232	166 (71.6[e])	203	124 (61.1[e])	1.17 [1.02; 1.34]; 0.021
GS5774-A[c]	52	46 (88.5[c])	36	22 (61.1)	1.45 [1.10; 1.91]; 0.003
Total[d]					1.22 [1.08; 1.38]; 0.002
+ study with moderate certainty of results[g]					
CAP-2	153	60 (39.2)	78	28 (35.9)	1.09 [0.77; 1.56]; 0.652
Total					Qualitative summary
Recovery at the end of the study					
Patients with LFO at start of treatment					
Studies with high certainty of results					
ACTT-1	232	206 (88.8[e])	203	156 (76.8[e])	1.16 [1.06; 1.26]; < 0.001
GS5774-A[c]	52	51 (98.1[c])	36	27 (75.0)	1.31 [1.08; 1.59]; < 0.001
Total[d]					1.18 [1.09; 1.28]; < 0.001
+ study with moderate certainty of results[g]					
CAP-2	150	106 (70.7)	77	49 (63.6)	1.11 [0.91; 1.35]; 0.322
Total					Qualitative summary

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

Mortality

Endpoint Sub-population Study	**Remdesivir + standard therapy**		**Placebo[a] + standard therapy**		**Remdesivir + standard therapy vs placebo[a] + standard therapy**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
Overall mortality (end of study)					
Patients with HFO / NIV at the start of treatment					
Studies with high certainty of results					
ACTT-1	95	19 (20.0)	98	20 (20.4)	0.98 [0.56; 1.72]; 0.997
GS5774-A[c]	3	0 (0)	2	0 (0)	–
Total					0.98 [0.56; 1.72]; 0.997

Morbidity

Endpoint Sub-population Study	**Remdesivir + standard therapy**		**Placebo[a] + standard therapy**		**Remdesivir + standard therapy vs placebo[a] + standard therapy**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
Recovery to day 14 / 15					
Patients with HFO / NIV at the start of treatment					
Studies with high certainty of results					
ACTT-1	95	40 (42.1[e])	98	33 (33.7[e])	1.25 [0.87; 1.80]; 0.246
GS5774-A[c]	3	0 (0)	2	1 (50.0)	0.25 [0.01; 4.23]; 0.375
Total[d]					1.20 [0.84; 1.72]; 0.319

Endpoint Sub-population Study	Remdesivir + standard therapy		Placebo[a] + standard therapy		Remdesivir + standard therapy vs placebo[a] + standard therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
Recovery at the end of the study					
Patients with HFO / NIV at the start of treatment					
Studies with high certainty of results					
ACTT-1	95	57 (60.0[e])	98	61 (62.2[e])	0.96 [0.77; 1.21]; 0.808
GS5774-A[c]	3	1 (33.3[c])	2	2 (100)	0.45 [0.12; 1.76]; 0.250
Total[d]					0.94 [0.75; 1.17]; 0.588

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

and

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

Health-related quality of life

Endpoints from this category were not collected.

Side effects

Endpoint	Remdesivir + standard therapy		Placebo[a] + standard therapy		Remdesivir + standard therapy vs placebo[a] + standard therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
Side effects					
AE (presented additionally)	No usable data available[f]				
SAEs	No usable data available[f]				

Endpoint	Remdesivir + standard therapy		Placebo[a] + standard therapy		Remdesivir + standard therapy vs placebo[a] + standard therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
Discontinuation because of AEs	No usable data available[f]				

[a] No placebo was administered in the GS5774-A study
[b] IQWiG calculation, unconditional exact test (CSZ method)
[c] Joint consideration of arms for remdesivir administration over 5 and 10 days
[d] Calculated from meta-analysis with fixed-effect, method according to Mantel-Haenszel
[e] IQWiG calculation
[f] High percentage of disease-related events (e.g. respiratory insufficiency)
[g] Separate analyses by ventilation status are not available for the CAP-2 study. However, since 83% of all patients received LFO at the start of the study, the entire study population will be included to assess the LFO sub-population. Since 17% of the patients were included incorrectly, the reliability of the results is rated as moderate.

Abbreviations used:
HFO: High-flow oxygen; LFO: Low-flow oxygen; n. d.: no data; CI: confidence interval; n: number of patients with (at least 1) event; N: Number of patients evaluated; NIV: non-invasive ventilation; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event

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 data on adolescents are available.

2. Number of patients or demarcation of patient groups eligible for treatment

COVID-19 infected adults and adolescents who have pneumonia requiring supplemental oxygen and are receiving low-flow or high-flow oxygen or non-invasive ventilation at start of treatment

approx. 45,000 – 79,000 patients

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.

4. Treatment costs

Annual treatment costs:

COVID-19 infected adults and adolescents who have pneumonia requiring supplemental oxygen and are receiving low-flow or high-flow oxygen or non-invasive ventilation at start of treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Remdesivir[a]	€ 3284.40 - € 6021.40
Therapy according to doctor's instructions	Patient-individual
Appropriate comparator therapy:	
Therapy according to doctor's instructions	Patient-individual
[a] Remdesivir is currently 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 package (information from the pharmaceutical company) plus 19 % value-added tax.	

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 September 2021.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 16 September 2021

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

Prof. Hecken