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
Casirivimab/ Imdevimab (COVID-19, ≥ 12 years)

of 6 October 2022

At its session on 6 October 2022, 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 D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Casirivimab/ Imdevimab in accordance with the resolution of 6 October 2022 (post-exposure prophylaxis of COVID-19):

Casirivimab/imdevimab

Resolution of: 6 October 2022
Entry into force on: 6 October 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 12 November 2021):

Ronapreve is indicated for treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Therapeutic indication of the resolution (resolution of 6 October 2022):

See therapeutic indication according to marketing authorisation.

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

a) Adults and adolescents aged 12 years and older 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, in the case of infection with a viral variant against which casirivimab/ imdevimab has insufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of casirivimab/ imdevimab compared to the appropriate comparator therapy:

An additional benefit is not proven.

b) Adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which casirivimab/imdevimab has sufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of casirivimab/ imdevimab compared to the appropriate comparator therapy:

Hint of a considerable additional benefit

c) Adolescents aged 12 years and older 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, in the case of infection with a viral variant against which casirivimab/ imdevimab has sufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of casirivimab/ imdevimab compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults and adolescents aged 12 years and older 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, in the case of infection with a viral variant against which casirivimab/ imdevimab has insufficient efficacy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	There are no usable data for the benefit assessment.
Morbidity	∅	There are no usable data for the benefit assessment.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	∅	There are no usable data for the benefit assessment.

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

No suitable data submitted.

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-48) unless otherwise indicated.

b) Adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which casirivimab/imdevimab has sufficient efficacy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall mortality
Morbidity	↑	Advantages of hospitalisation due to COVID-19 and reduction of COVID-19 symptoms
Health-related quality of life	∅	No data available.
Side effects	n.a.	There are no usable data for the benefit assessment.

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
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n.a.: not assessable

COV-2067[a] study: adaptive, placebo-controlled, double-blind, randomised phase I/II/III study; direct comparison: Casirivimab/ imdevimab vs placebo

Patients in cohort 1 randomised under protocol amendments 6 and 7 by 24.02.2021 (data cut-off from 19.08.2021).

Mortality

COV-2067 study Endpoint	Casirivimab/ imdevimab		placebo		Casirivimab/ imdevimab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[b]
Mortality (until day 169)					
Overall mortality	1192	1 (0.1)	1193	7 (0.6)	0.14 [0.02; 1.16]; 0.035[c]

Morbidity

COV-2067 study Endpoint	Casirivimab/ imdevimab		placebo		Casirivimab/ imdevimab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[b]
Morbidity (until day 29)					
Hospitalisation due to COVID-19	1192	11 (0.9)	1193	40 (3.4)	0.28 [0.14; 0.53]; < 0.001
Admission to an intensive care unit due to COVID-19	1192	3 (0.3)	1193	9 (0.8)	0.33 [0.09; 1.23]; 0.086

COV-2067 study Endpoint	Casirivimab/ imdevimab		placebo		Casirivimab/ imdevimab vs placebo
	N	Median time to event in days [95% CI] Patients with event n (%)	N	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI] p value[d]
Morbidity (until day 29)					
Reduction of COVID-19 symptoms (SE-C19)[e]	1192	10.0 [9.0; 11.0][f] 683 (57.3)	1193	13.0 [12.0; 15.0][f] 591 (49.5)	1.27 [1.14; 1.42]; < 0.001
Return to normal health	no usable data available[g]				
Return to normal activities	no usable data available[g]				
Health status (EQ 5D VAS)	no usable data available[g]				

Health-related quality of life

not assessed

Side effects

COV-2069 study Endpoint	Casirivimab/ imdevimab		placebo		Casirivimab/ imdevimab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[b]
AEs (presented additionally)	no usable data available[h]				
SAEs	no usable data available[i]				
Severe AEs[j]	no usable data available[i]				
Discontinuation due to AEs	no usable data available[h]				
Infusion-related reactions	no usable data available[k]				
Other specific AEs	no usable data available[l]				

[a] The COV-2067 study is an adaptive phase 1/2/3 study; phase 3 of the study relevant for the benefit assessment is shown from protocol amendment 6 (14.11.2020).
[b] IQWiG calculation, unconditional exact test (CSZ method)
[c] Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods.
[d] Effect and CI: Cox proportional hazards model with treatment and country as fixed effects; p value: Log-rank test stratified by country
[e] Patients with a raw score ≤ 3 across all symptoms at the start of the study were censored
[f] Discrepancy between information in module 4 B and module 5 of the dossier. The data presented are from the study report.
[g] Insufficient return rates
[h] Not systematically collected in the study
[i] The pharmaceutical company does not provide any information on the events which it classifies as disease-related
[j] Operationalised as CTCAE grade ≥ 3
[k] No usable data available, as it remains unclear how infusion-related reactions were collected in the study
[l] No other specific AEs were identified based on the SAEs or severe AEs that occurred in the relevant study. AEs were not systematically collected in the relevant study; a selection of specific AEs based on the AEs that occurred is therefore not possible.

Abbreviations used:
COVID-19: Coronavirus disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; CI: confidence interval; mFAS: Modified Full Analysis Set; n: number of patients with (at least 1) event; N: number of randomised patients of the mFAS population; PC: pharmaceutical company; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event

c) Adolescents aged 12 years and older 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, in the case of infection with a viral variant against which casirivimab/ imdevimab has sufficient efficacy

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No suitable data submitted.

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

Adults and adolescents aged 12 years and older 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, in the case of infection with a viral variant against which casirivimab/ imdevimab has insufficient efficacy

0 patients

Adults and adolescents aged 12 years and older 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, in the case of infection with a viral variant against which casirivimab/ imdevimab has sufficient efficacy

0 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 Ronapreve (combination of active ingredients: casirivimab/ imdevimab) at the following publicly accessible link (last access: 11 July 2022):

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

For casirivimab/ imdevimab, no sufficient efficacy could be demonstrated against variants of the Omicron virus[2] circulating alone in Germany at the time of passing the resolution using *in vitro* neutralisation tests.

4. Treatment costs

Annual treatment costs:

Adults and adolescents aged 12 years and older 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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Casirivimab/ imdevimab	Incalculable
Appropriate comparator therapy:	
Therapy according to doctor's instructions	Different from patient to patient

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 6 October 2022.

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

Berlin, 6 October 2022

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

Prof. Hecken

[2] RKI weekly situation report on the coronavirus disease-2019 (COVID-19) (15.09.2022)