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 Sotrovimab (COVID-19, ≥ 12 years)

of 3 November 2022

At its session on 3 November 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. Annex XII shall be amended in alphabetical order to include the active ingredient Sotrovimab as follows:

Sotrovimab

Resolution of: 3 November 2022
Entry into force on: 3 November 2022
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 17 December 2021):

Xevudy is indicated for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19.

Therapeutic indication of the resolution (resolution of 3 November 2022):

See therapeutic indication according to marketing authorisation.

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

a) Adults with COVID-19 disease who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which sotrovimab has a considerably reduced or insufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

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

An additional benefit is not proven.

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

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of sotrovimab compared to therapy according to the doctor's instructions:

Hint for a considerable additional benefit

c) Adolescents aged 12 to < 18 years weighing at least 40 kg with COVID-19 who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19

Appropriate comparator therapy:

Therapy according to doctor's instructions

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

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults with COVID-19 disease who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which sotrovimab has a considerably reduced or 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.c.: not calculable

No suitable data submitted.

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-56) unless otherwise indicated.

b) Adults with COVID-19 who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which sotrovimab 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 in disease progression, admissions to the intensive care unit and hospitalisation due to any cause
Health-related quality of life	n.c.	There are no usable data for the benefit assessment.
Side effects	↔	No relevant differences 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.c.: not calculable		

COMET-ICE study: placebo-controlled, double-blind, randomised phase I/II/III study; direct comparison: Sotrovimab vs placebo

Mortality

COMET-ICE study Endpoint Time	Sotrovimab		Placebo		Sotrovimab vs placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value
Overall mortality[b] Day 90	528	0 (0[c])	529	4 (0.8[c])	–[d]; 0.047[e]

Morbidity

COMET-ICE study Endpoint Time	**Sotrovimab**		**Placebo**		Sotrovimab vs placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value
Development of severe and/or critical respiratory COVID-19[f,g]					
Day 29	528	7 (1.3[c])	529	26 (4.9[c])	0.27 [0.12; 0.62][c]; < 0.001[e]
Category 2[h]	528	7 (1.3[c])	529	12 (2.3[c])	–
Category 3[i]	528	0 (0[c])	529	10 (1.9[c])	–
Category 4[j]	528	0 (0[c])	529	4 (0.8[c])	–
Hospitalisation of any duration due to non-respiratory complications from COVID-19[f,g]					
Day 29	528	4 (0.8[c])	529	4 (0.8[c])	1.00 [0.25; 3.99][c]; > 0.999[e]
Hospitalisation > 24 h due to any cause[g]					
Day 29	*528*	*6 (1.2[c])*	*529*	*29 (5.5[c])*	*0.21 [0.09; 0.50][c]; < 0.001[e]*
Hospitalisation of any duration due to any cause ***(presented additionally)[g]***					
Day 29	*528*	*7 (1.3[c])*	*529*	*29 (5.5[c])*	*0.24 [0.11; 0.55][c]; < 0.001[e]*
Day 90	*528*	*11 (2.1[c])*	*529*	*31 (6.0[c])*	*0.36 [0.18; 0.70][c]; 0.002[e]*
Admission to an intensive care unit due to any cause[g]					
Day 29	528	0 (0[c])	529	9 (1.7[c])	0.05 [< 0.01;0.90][c]; 0.003[e]

Health-related quality of life

COMET-ICE study Endpoint Time	**Sotrovimab**		**Placebo**		Sotrovimab vs placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value
SF-12	No usable data available				

Side effects

COMET-ICE study Endpoint Time	Sotrovimab		Placebo		Sotrovimab vs placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI] p value
AEs (presented additionally)[k]	523	128 (24.5)	526	121 (23.0)	–
SAEs[k]	523	9 (1.7)	526	18 (3.4)	0.50 [0.23; 1.11]; 0.084[e]
Severe AEs[k,l]	523	21 (4.0)	526	28 (5.3)	0.75 [0.43; 1.31]; 0.331[e]
Discontinuation due to AEs[m]	523	0 (0)	526	0 (0)	_
infusion-related reactions (AEs)	523	7 (1.3)	526	6 (1.1)	1.17 [0.40; 3.47]; 0.846[e]
Infusion-related reactions (SAEs)	523	0 (0)	526	0 (0)	_

[a] Number of randomised patients. Values based on other patient numbers are marked in the corresponding line if deviation is relevant
[b] In the control arm, one additional death was recorded as a fatal SAE during the course of the study after 90 days. The reason given was completed suicide.
[c] IQWiG calculation
[d] Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods; no presentation of effect estimate and CI, as not informative
[e] IQWiG calculation, unconditional exact test (CSZ method)
[f] The pharmaceutical company (PU) presents evaluations in Module 4 A in which 2 patients in the placebo arm who died before day 29 were counted as an event. It is not clear from the study documents whether these patients had experienced the relevant event before death. The patients were therefore not counted as an event for the present benefit assessment.
[g] In Module 4 A, the pharmaceutical company presents evaluations for which the corresponding patients were evaluated as having an event in the case of missing values. For the present benefit assessment, IQWiG performed its own calculations without substituting missing values.
[h] Low flow nasal cannula/ face mask
[i] Mask without resuscitation or high-flow nasal cannula/ non-invasive ventilation (including continuous positive airway pressure support)
[j] Mechanical ventilation/ ECMO
[k] Overall rate excluding events, classified by the pharmaceutical company as disease-related
[l] Operationalised as DAIDS grade ≥ 3
[m] Discontinuations of therapy due to AEs are shown; in Module 4 A, the pharmaceutical company presents results on discontinuations of the study due to AEs. In the placebo arm of the study, 5 patients discontinued the study due to AEs, whereby the company classified the AEs for 2 patients as disease-related.

Abbreviations used:
DAIDS: Division of Acquired Immunodeficiency Syndrome; ECMO: extracorporeal membrane oxygenation; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; RCT: randomised controlled trial; RR: relative risk; SF-12: short form-12-item health survey; SAE: serious adverse event; AE: adverse event

c) Adolescents aged 12 to < 18 years weighing at least 40 kg with COVID-19 who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
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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 oxygen therapy and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which sotrovimab has a considerably reduced or insufficient efficacy

0 patients[2]

Adults and adolescents aged 12 years and older weighing at least 40 kg with COVID-19 who do not require oxygen therapy and who are at increased risk of progressing to severe COVID-19, in the case of infection with a viral variant against which sotrovimab has sufficient efficacy

0 patients

[2] In patients with relevant immunosuppression and/or prolonged viral excretion, the use of sotrovimab as combination therapy with virustatics can be considered in individual cases.

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 Xevudy (active ingredient: sotrovimab) at the following publicly accessible link (last access: 25 October 2022):

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

For sotrovimab, considerably reduced efficacy could be demonstrated against variants of the Omicron virus[3] circulating alone in Germany at the time of passing the resolution using *in vitro* neutralisation tests. This variant was not investigated in the pivotal COMET-ICE study. The majority of the study participants examined were infected with the wild-type virus and other virus variants detected included the alpha variant and the epsilon variant.

4. Treatment costs

Annual treatment costs:

Adults and adolescents aged 12 years and over with COVID-19 who do not require oxygen supplementation and are at increased risk of progressing to severe COVID-19

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Sotrovimab Additionally required SHI services Total:	€ 2,990.17 € 360.00 € 3,350.17
Appropriate comparator therapy:	
Therapy according to doctor's instructions	Different from patient to patient

Costs after deduction of statutory rebates (information from the pharmaceutical company)

[3] RKI weekly situation report on the coronavirus disease-2019 (COVID-19) (20.10.2022)

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 3 November 2022.

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

Berlin, 3 November 2022

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

Prof. Hecken