Gemeinsamer Bundesausschuss

Tixagevimab/ cilgavimab (first dossier requirement: COVID-19, increased risk of severe course, ≥ 12 years)

Resolution of: 20 April 2023 Valid until: unlimited
Entry into force on: 20 April 2023
Federal Gazette, BAnz AT 21 06 2023 B3

New therapeutic indication (according to the marketing authorisation of 16 September 2022):

EVUSHELD is indicated for the treatment of 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.

Therapeutic indication of the resolution (resolution of 20 April 2023):

See new 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 tixagevimab/ cilgavimab has a considerably reduced or no sufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of tixagevimab/ cilgavimab 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 tixagevimab/ cilgavimab has sufficient efficacy

Appropriate comparator therapy:

Therapy according to doctor's instructions

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

Hint for a minor 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 tixagevimab/ cilgavimab 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 tixagevimab/ cilgavimab has a considerably reduced or no sufficient efficacy

No suitable data submitted.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

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
∅: No data available.
n.a.: not assessable

[1] Data from the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-111) 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 tixagevimab/ cilgavimab has sufficient efficacy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑	Advantages in the endpoints of severe COVID-19 and hospitalisation due to any cause.
Health-related quality of life	∅	No data available.
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 ∅: No data available. n.a.: not assessable		

TACKLE study: placebo-controlled, double-blind, randomised phase I/II/III study; direct comparison: Tixagevimab/ cilgavimab vs placebo

Mortality

TACKLE study **Endpoint** **Time period**	**Tixagevimab/ cilgavimab**		**Placebo**		Tixagevimab/ cilgavimab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Overall mortality until day 169	399	4 (1.0)	407	6 (1.5)	0.68 [0.19; 2.39]; 0.547

Morbidity

TACKLE study Endpoint Time period	**Tixagevimab/ cilgavimab**		**Placebo**		Tixagevimab/ cilgavimab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Severe COVID-19[b]					
until day 29	410	16 (3.9)	419	37 (8.8)	0.44 [0.25; 0.78]; 0.005
Severe respiratory failure (presented additionally)[c]					
until day 29	*413*	*3 (0.7)*	*421*	*11 (2.6)*	*0.28 [0.08; 0.996]; 0.049*
Admission to an intensive care unit due to any cause					
until day 29	413	6 (1.5)	421	11 (2.6)	0.56 [0.21; 1.48]; 0.240
Hospitalisation due to any cause					
until day 169	413	28 (6.8)	421	48 (11.4)	0.59 [0.38; 0.93]; 0.022
COVID-19 symptomatology					
No suitable data					

TACKLE study Endpoint Time period	**Tixagevimab/ cilgavimab**		**Placebo**		Tixagevimab/ cilgavimab vs placebo
	N	Median time to event in days [95% CI] Patients with event n (%)	N[a]	Median time to event in days [95% CI] Patients with event n (%)	HR [95% CI]; p value[d]
Return to normal health					
until day 29	413	29 [27; 29] 270 (65.4)	421	29 [n.c.; n.c.] 266 (63.2)	1.12 [0.95; 1.33]; 0.190

Health-related quality of life

Endpoint not surveyed.

Side effects

TACKLE study Endpoint	**Tixagevimab/ cilgavimab**		**Placebo**		Tixagevimab/ cilgavimab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
AEs (presented additionally)[e]	413	136 (32.9)	421	147 (34.9)	-
SAEs[e]	413	13 (3.1)	421	13 (3.1)	1.03 [0.48; 2.19]; 0.947
Severe AEs[e]	No suitable data				
Discontinuation due to AEs[f]	413	0 (0)	421	0 (0)	-
Hypersensitivity reactions and reactions at the injection site	No suitable data				

[a] CMH method stratified by time since onset of symptoms (≤ 5 days vs > 5 days) and risk of progressing to severe COVID-19 (high vs low)
[b] Operationalised as the presence of pneumonia (fever, cough, tachypnoea or dyspnoea and pulmonary infiltrates), hypoxaemia (oxygen saturation < 90% in indoor air and/or severe dyspnoea), or a WHO clinical progression scale score for COVID-19 of 5 or higher
[c] Defined as the need for mechanical ventilation, ECMO, non-invasive ventilation, or oxygen delivery via a high-flow nasal cannula
[d] Cox model stratified by time since onset of symptoms (≤ 5 days vs > 5 days) and risk of progressing to severe COVID-19 (high vs low)
[e] Overall rate excluding events, classified by the pharmaceutical company as disease-related. However, due to the wide-ranging COVID-19 symptomatology, inclusion of other events that can be both side effects and symptomatology of the underlying disease is obvious.
[f] Shown are discontinuations of therapy due to AEs; in module 4A, the pharmaceutical company presents results on discontinuations of the study due to AEs for the TACKLE study (3 [0.7%] vs 7 [1.7%]).

Abbreviations used:
CMH: Cochran-Mantel-Haenszel; COVID-19: coronavirus disease 2019; HR: hazard ratio; KI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; n.c.: not calculable; RCT: randomised controlled trial; RR: relative risk; 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

No suitable data submitted.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
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∅: No data available.
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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 tixagevimab/ cilgavimab has a considerably reduced or no sufficient 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 tixagevimab/ cilgavimab has sufficient efficacy

0 patients

[2] In patients with relevant immunosuppression and/or prolonged viral excretion, the use of tixagevimab/ cilgavimab as combination therapy with virustatics can be considered in specific cases, provided that tixagevimab/ cilgavimab is not assessed as ineffective against the predominant or proven viral variant.

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 Evusheld (active ingredient: tixagevimab/ cilgavimab) at the following publicly accessible link (last access: 10 February 2023):

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

For tixagevimab/ cilgavimab, a significantly reduced (BA.1, BA.4, BA.5) or no (BQ.1/BQ.1.1, BA.4.6, BF.7. XBB) efficacy against the omicron viral variants[3] circulating in Germany at the time of drafting the resolution was demonstrated by *in vitro* neutralisation tests. These variants were not investigated in the label-enabling TACKLE study. The study participants examined were predominantly infected with the viral variants alpha, B.1.1.519, gamma and delta.

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 oxygen therapy 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:	
Tixagevimab/ cilgavimab	€ 4,511.92
Additionally required SHI services	€ 360.00
Total	€ 4,871.92
Therapy according to doctor's instructions	Different from patient to patient
Appropriate comparator therapy:	
Therapy according to doctor's instructions	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 30.06.2016)

Costs for additionally required SHI services: not applicable

[3] RKI weekly situation report on the coronavirus disease-2019 (COVID-19) (02.03.2023)

5. Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Tixagevimab/ cilgavimab

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with tixagevimab/ cilgavimab for the treatment of COVID-19 on the basis of the marketing authorisation granted under Medicinal Products Act:

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 tixagevimab/ cilgavimab has a considerably reduced or no sufficient efficacy

   – No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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 tixagevimab/ cilgavimab has sufficient efficacy

   – No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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

   – No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.