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:
Icosapent ethyl (dyslipidaemia, pretreated patients)

of 17 February 2022

At its session on 17 February 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 Icosapent ethyl as follows:

Icosapent ethyl

Resolution of: 17 February 2022
Entry into force on: 17 February 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 26 March 2021):

Vazkepa is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥ 150 mg/dL [≥ 1.7 mmol/L]) and:

- established cardiovascular disease, or

- diabetes, and at least one other cardiovascular risk factor.

Therapeutic indication of the resolution (resolution of 17 February 2022):

see therapeutic indication according to marketing authorisation.

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

<u>Adults with elevated triglycerides (≥ 150 mg/dl) and high cardiovascular risk to reduce the risk of cardiovascular events</u>

Appropriate comparator therapy:

- Therapy according to doctor's instructions taking into account statins and cholesterol absorption inhibitors

Extent and probability of the additional benefit of Icosapent ethyl in combination with statin compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with elevated triglycerides (≥ 150 mg/dl) and high cardiovascular risk to reduce the risk of cardiovascular events

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment. Advantage in the combined endpoint MACE, in detail in the individual components "cardiovascular death", "non-fatal myocardial infarction" and "non-fatal stroke", which, however, cannot be assessed due to uncertainties.
Health-related quality of life	∅	No data available.
Side effects	↔	No relevant differences for the benefit assessment. In detail, disadvantage in the specific AE "Haemorrhages".

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

REDUCE-IT study: Icosapent ethyl vs placebo (each in addition to statin plus ezetimibe if required)

Mortality

Endpoint	Icosapent ethyl (+ statin + possibly ezetimibe)		Placebo (+ statin + possibly ezetimibe)		Intervention vs control
	N	Median survival time in months [95 % CI] Patients with event n (%)	N	Median survival time in months [95 % CI] Patients with event n (%)	HR[a] [95 % CI] p value[b] Absolute difference (AD)[e]
Overall mortality	4089	n.d. 274 (6.7)	4090	n.d. 310 (7.6)	0.87 [0.74; 1.02]; 0.092

[1] Data from the dossier assessment of the IQWiG (A21-113) and from the addendum (A22-03), unless otherwise indicated.

Morbidity

Endpoint	Icosapent ethyl (+ statin + possibly ezetimibe)		Placebo (+ statin + possibly ezetimibe)		Intervention vs control
	N	Median survival time in months [95 % CI] Patients with event n (%)	N	Median survival time in months [95 % CI] Patients with event n (%)	HR[a] [95 % CI] p value[b] Absolute difference (AD)[e]
MACE[c]	4089	n.d. 459 (11.2)	4090	n.d. 606 (14.8)	0.74 [0.65; 0.83]; < 0.001 AD = 3.6%
Cardiovascular death[d]	4089	n.d. 174 (4.3)	4090	n.d. 213 (5.2)	0.80 [0.66; 0.98]; 0.032
Non-fatal myocardial infarction[d]	4089	n.d. 237 (5.8)	4090	n.d. 332 (8.1)	0.70 [0.59; 0.82]; < 0.001 AD = 2.3%
Non-fatal stroke[d]	4089	n.d. 85 (2.1)	4090	n.d. 118 (2.9)	0.71 [0.54; 0.94]; 0.015 AD = 0.8%
Total hospitalisation	No data available.				

Health-related quality of life

Quality of life was not assessed in the REDUCE-IT study.

Side effects

Endpoint	Icosapent ethyl (+ statin + possibly ezetimibe)		Placebo (+ statin + possibly ezetimibe)		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[f] Absolute difference (AD)[e]
Total adverse events *(presented additionally)*	4089	3343 (81.8)	4090	3326 (81.3)	-
Serious adverse events (SAE)	4089	1252 (30.6)	4090	1254 (30.7)	1.00 [0.94; 1.07]; 0.982
Therapy discontinuation due to adverse events	4089	321 (7.9)	4090	335 (8.2)	0.96 [0.83; 1.11]; 0.682
Specific adverse events					
Rhabdomyolysis (PT, AEs)	4089	3 (0.1)	4090	6 (0.1)	0.50 [0.13; 2.00][g]; 0.352
Haemorrhages (SMQ, AEs)[h]	4089	482 (11.8)	4090	404 (9.9)	1.19 [1.05; 1.35]; 0.006 AD = 1.9%
Haemorrhages (SMQ, SAEs)[h]	4089	111 (2.7)	4090	85 (2.1)	1.31 [0.99; 1.73]; 0.071
Severe liver toxicity (SMQ, SAEs)[i]	4089	16 (0.4)	4090	12 (0.3)	1.33 [0.63; 2.82]; 0.532

a. HR and CI: Cox proportional hazards model stratified by stratification factors at randomisation (cardiovascular risk category [secondary prevention; primary prevention], geographic region, use of ezetimibe)
b. p value: Log-rank test stratified by stratification factors at randomisation
c. MACE: major adverse cardiovascular event, combined cardiovascular endpoint composed of the components cardiovascular death, non-fatal myocardial infarction and non-fatal stroke
d. All events in the entire course of the study have been presented and not the events included in the combined endpoint
e. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
f. IQWiG calculation, unconditional exact test (CSZ method according to [7])
g. IQWiG calculation of RR and CI (asymptotic)
h. Operationalised as the following SMQs (coded according to MedDRA): "Gastrointestinal bleeding (SMQ)", "Central nervous system haemorrhage and cerebrovascular conditions (SMQ)" and "Haemorrhage terms (excl. laboratory terms) (SMQ)"
i. Operationalised as SMQ "Hepatic disorders" (coded according to MedDRA)

Endpoint	Icosapent ethyl (+ statin + possibly ezetimibe)		Placebo (+ statin + possibly ezetimibe)		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[f] Absolute difference (AD)[e]
Abbreviations used: AD = absolute difference; HR = hazard ratio; n.d. = no data; CI = confidence interval; MACE = major adverse cardiovascular events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; PT = preferred term; RR = relative risk; SMQ = standardised MedDRA query; SAE = serious adverse event; AE = adverse event; vs = versus					

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

Adults with elevated triglycerides (≥ 150 mg/dl) and high cardiovascular risk to reduce the risk of cardiovascular events

Approx. 844,000 to 878,000 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 Vazkepa (active ingredient: icosapent ethyl) at the following publicly accessible link (last access: 5 January 2022):

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

4. Treatment costs

Adults with elevated triglycerides (≥ 150 mg/dl) and high cardiovascular risk to reduce the risk of cardiovascular events

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Icosapent ethyl	€ 3,079.99
+ Simvastatin[2]	€ 53.62 - € 99.06
Total:	€ 3,133.61 - € 3,179.05

[2] Simvastatin is shown as an example for the group of statins with a dosage range of 20 - 80 mg.

Appropriate comparator therapy:	
Monotherapy	
Simvastatin[2]	€ 53.62 - € 99.06
Combination therapy	
Simvastatin[2] + Ezetimibe	€ 203.93 - € 249.30[3]

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2022

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 17 February 2022.

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

Berlin, 17 February 2022

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

Prof. Hecken

[3] For reasons of the principle of economic efficiency, the range is made up of a combination of the mono-preparations with 10 mg ezetimibe and 20 mg simvastatin (= lower limit), as well as the fixed combination of 10 mg ezetimibe / 80 mg simvastatin (= upper limit).