Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient icosapent ethyl in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 September 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 27 August 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 December 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of icosapent ethyl compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements

submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of icosapent ethyl.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Icosapent ethyl (Vazkepa) according to the product information

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 17.02.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

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

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant advantage shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to icosapent ethyl, statins, fibrates, ezetimibe, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors as well as combination medicinal products (statin/ezetimibe) are approved for the treatment of adults with high cardiovascular risk and elevated triglyceride levels.

on 2. Non-medicinal treatments are not considered as an appropriate comparator therapy for the present therapeutic indication.

on 3. The following resolutions of the G-BA are relevant for the present therapeutic indication:

Annex III of the AM-RL (prescription restrictions and exclusions)
- No. 35. Lipid-lowering agents
- No. 35a. Evolocumab
- No. 35b. Alirocumab

Annex IV of the AM-RL (therapeutic information)
- Therapeutic information on ezetimibe of 17 December 2009 was revoked by resolution of 22 November 2018
- IQWiG Rapid Report on ezetimibe

Annex XII of the AM-RL (benefit assessment Section 35a SGB V)
- Evolocumab (resolutions of 2 September 2018 and 9 March 2016)
- Alirocumab (resolutions of 2 May 2019 and 4 May 2016)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

The present therapeutic indication consists of reducing the risk of cardiovascular events in adults with hypertriglyceridaemia who are at high risk of cardiovascular events (due to established cardiovascular disease or diabetes and at least one other cardiovascular

risk factor). In the guidelines and the current written opinion of the scientific-medical societies, ezetimibe in particular is recommended in addition to statins to reduce the cardiovascular risk in patients with elevated triglycerides and high cardiovascular risk. Although the current written opinion of the scientific-medical societies also mentions PCSK9 inhibitors as a possible option for reducing cardiovascular risk, PCSK9 inhibitors cannot be prescribed for these patients according to Annex III of the Pharmaceuticals Directive since the dietary and medicinal lipid-lowering therapies have not yet been exhausted in the present therapeutic indication and thus, there is also no indication for LDL apheresis. Furthermore, the two active ingredients evolocumab and alirocumab were unable to show any additional benefit in the benefit assessment according to Section 35a SGB V. For these reasons, the PCSK9 inhibitors are not considered as options for the appropriate comparator therapy.

The evidence also recommends treatment of the underlying disease(s), possible secondary causes of hypertriglyceridaemia and also lifestyle measures. Although not with the explicit purpose of reducing cardiovascular risks, fibrates are recommended in patients with severe hypertriglyceridaemia or with mixed hyperlipidaemia and elevated triglycerides. Since the approved therapeutic indication for Vazkepa includes patients with cardiovascular risk or cardiovascular disease, the G-BA does not consider fibrates to be part of the appropriate comparator therapy, particularly in view of the current opinion of the scientific-medical societies.

Against this background, the G-BA has determined a "therapy according to doctor's instructions, taking into account statins and cholesterol absorption inhibitors" as the appropriate comparator therapy for adults with elevated triglycerides (≥ 150 mg/dL) and high cardiovascular risk to reduce the risk of cardiovascular events.

The therapy according to doctor's instructions can also include the combination of both product classes mentioned; It is assumed that comparable treatment regimens are used in the intervention arm and the comparator arm (fair comparison of the lipid-lowering agents used, dosages, etc.).
It is assumed that a guideline-compliant, patient-individual treatment of the known cardiovascular disease and the corresponding underlying diseases or risk factors such as hypertension, cardiac arrhythmias, diabetes mellitus, hypercholesterolaemia as well as the concomitant symptoms is carried out in both study arms. The current German health care context must be taken into account accordingly. Accordingly, it should be possible to adjust the basic/concomitant medication to the respective needs of the patient in both study arms. Therapy adjustment may include dosage adjustments as well as changes of therapy or therapy initiation for the treatment of new symptoms as well as for the deterioration of existing symptoms.
Any secondary causes that are significant for the hypertriglyceridaemia must be treated accordingly.
The requirements of the Pharmaceuticals Directive Annex III (prescription restrictions and exclusions, No. 35, lipid-lowering agents, No. 35a, evolocumab, No. 35b, alirocumab) as well as the marketing authorisations and product information of the medicinal products must be observed.

Change of the appropriate comparator therapy

As the present therapeutic indication for icosapent ethyl does not explicitly address patients who do not achieve target LDL-C levels with maximum tolerated statin therapy, it is assumed that maximum tolerated medicinal therapy is not indicated for all patients. Against this background, the G-BA changed the appropriate comparator therapy in the

procedure, also taking into account the statements. However, the unchanged continuation of an inadequate therapy does not correspond to the appropriate comparator therapy. Against this background, it must be demonstrated that any existing treatment options are unsuitable or have been exhausted.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of icosapent ethyl is assessed as follows:

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

An additional benefit is not proven.

Justification:

For the benefit assessment according to Section 35a SGB V, the pharmaceutical company submits the randomised, double-blind, multicentre REDUCE-IT study, which investigates the administration of icosapent ethyl versus placebo, in each case in combination with statins and, if required, ezetimibe, in adults with existing cardiovascular disease or high cardiovascular risk and elevated triglyceride levels.

On the one hand, patients with a high risk of cardiovascular diseases (primary prevention, approx. 30%) were enrolled: Patients aged ≥ 50 years with diabetes mellitus (type 1 or type 2) requiring medicinal treatment and at least one of the following additional cardiovascular risk factors: advanced age (men ≥ 55 years, women ≥ 65 years), smoking, hypertension, low high-density lipoprotein cholesterol (HDL-C) level (men ≤ 40 mg/dl, women ≤ 50 mg/dl), elevated high-sensitivity C-reactive protein, renal dysfunction, retinopathy, micro or macroalbuminuria or Ankle Brachial Index (ABI) < 0.9. On the other, patients aged ≥ 45 years with a very high risk of cardiovascular disease, i.e., with proven cardiovascular disease (secondary prevention, approx. 70%) were enrolled. Proven cardiovascular disease was defined as the presence of at least one of the following events: coronary artery disease, cerebrovascular disease or carotid artery disease or peripheral arterial disease (PAD).

The enrolled patients should have a low-density lipoprotein cholesterol (LDL-C) value between 40 and 100 mg/dl and a fasting triglyceride value between 135 and 500 mg/dl 28 days before randomisation under stable therapy with statins and, if required, ezetimibe. Stable therapy was defined as a consistent daily statin dose of the same statin plus (if required) a consistent daily ezetimibe dose. During the course of the study, the lower limit of the triglyceride value was raised from 135 to 200 mg/dl in order to increase the enrolment of patients with values ≥ 200 mg/dl.

A total of 8,179 patients were randomised in a 1:1 ratio to treatment with icosapent ethyl or placebo. Randomisation was stratified by primary or secondary prevention, geographic region and ezetimibe intake.

From the time of randomisation, patients received either 2 g of icosapent ethyl or mineral oil (as placebo) orally as a soft capsule 2-times daily in addition to their stable background therapy of statin and, if required, ezetimibe. Therapy adjustment (i.e., increase in statin dose or additional administration of ezetimibe) was possible during the course of the study if an LDL-C value of 130 mg/dl was exceeded in two consecutive measurements at least one week apart.

The primary endpoint of the REDUCE-IT study was the combined endpoint consisting of cardiovascular death, non-fatal myocardial infarction (MI, including silent MI), non-fatal stroke, coronary revascularisation and unstable angina attributed to myocardial ischaemia requiring emergency hospitalisation according to invasive/ non-invasive examination. Other patient-relevant endpoints were assessed in the categories of mortality, morbidity and side effects.

The end of the study was event-driven. The individual treatment and observation periods of the patients varied; the median observation period in both treatment arms of the REDUCE-IT study was 4.9 years.

Implementation of the appropriate comparator therapy

The G-BA determined a "therapy according to doctor's instructions, taking into account statins and cholesterol absorption inhibitors". In addition, it should be possible to adjust the basic or concomitant medication to the respective needs of the patient in both study arms.

The included patient population should have LDL-C levels between 40 and 100 mg/dl at the start of the study on stable statin therapy (± ezetimibe). The statin therapy including the dosage should be in place for at least 28 days before the start of the study and should be maintained until the end of the study, except in the case of adverse events or lack of efficacy. The efficacy is assessed according to guidelines,[2] among other things, on the basis of the LDL-C levels of the patients. However, in the present study, the principal investigators were blinded to the LDL-C levels of the patients during the course of the study, and the principal investigators were only unblinded to the LDL-C values when the LDL-C values were > 130 mg/dl in two consecutive measurements. It was then possible to either increase the dose of the existing statin or to consider the additional administration of ezetimibe in the sense of an emergency therapy.

At the start of the study, the majority of patients (62 - 63%) received medium and about one-third received high statin doses; about 6% also received ezetimibe. Thus, the median LDL-C levels in both study arms at the start of the study were around 74 - 75 mg/dl[3]. Apart from a slight increase in LDL-C levels in the comparator arm shortly after the start of the study, these remained largely unchanged in the median over the course of the study in both study arms. Therapy optimisations with regard to LDL-C-lowering therapy were only carried out to a small extent in the study: The information in the other study documents on concomitant medication shows that in both study arms, approx. 25% of the patients with a low statin dose at the start of the study received a dose increase to a moderate or high dose in the further

[2] ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS): Mach F, Baigent C, Catapano AL et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41(1): 111-188. https://dx.doi.org/10.1093/eurheartj/ehz455

[3] The median LDL-C levels were [1st quartile; 3rd quartile] 74.0 mg/dl [61.0; 88.0] in the icosapent ethyl and 75.0 mg/dl [63.0; 89.0] in the control arm.

course of the study. Throughout the study, 38% of patients in the icosapent ethyl arm and 40% in the control arm received statins at a high dosage and 8% of patients in both arms received ezetimibe as additional therapy. It is not clear from the documents submitted by the pharmaceutical company to what extent the remaining therapy options were not suitable or exhausted for the remaining patients. Therefore, overall, it is uncertain whether further escalations of statin or ezetimibe therapy would have been equally necessary or possible in each of the two study arms to achieve further LDL-C lowering and LDL-C lowering-related reductions in cardiovascular events in each of the two arms.

The current ESC/EAS guideline[2] clearly states that for patients at high and very high risk of cardiovascular disease, in addition to weight reduction and lifestyle changes, lowering LDL-C levels is of central importance for reducing this risk. LDL-C target levels < 70 mg/dl are recommended for patients at high risk of cardiovascular events, and LDL-C target levels < 55 mg/dl for patients at very high risk. The National Health Care Guideline[4] also states that further escalation with ezetimibe can be considered as an option, especially if high statin doses are not tolerated or if target levels < 70 mg/dl are not reached under the maximum tolerated statin dose. However, the patients already had median LDL-C levels of 74-75 mg/dl at the start of the study and these remained largely unchanged in both study arms over the course of the study. A further reduction to < 70 mg/dl or < 55 mg/dl could still have been achieved in the REDUCE-IT study, for example, by escalation with ezetimibe. In the written statement procedure, it was stated that the LDL-C levels to which the patients were adjusted at the start of the REDUCE-IT study were largely within an acceptable range. However, from the clinicians' point of view, further escalation options, such as the use of ezetimibe, should be considered for patients at high and very high risk of cardiovascular disease. Data from the pharmaceutical company show that the percentage of subjects with LDL-C levels < 55 mg/dl at the start of the study was about 13%[5].

After the oral hearing, the pharmaceutical company submitted further data in the context of the written statement procedure on the percentages of those patients in the REDUCE-IT study who had an LDL-C level below 40 mg/dl, above 100 mg/dl (or 100 to 130 mg/dl) and above 130 mg/dl in the course of the study. However, the percentages presented by the pharmaceutical company are underestimated, as the observation periods in the study varied from patient to patient and the number of patients at risk decreased significantly as early as one year after randomisation and also in the further course of the study. The data[6] show that about one year after the start of the study, about 19% of the patients in the icosapent ethyl arm and about 26% in the control arm had LDL-C levels > 100 mg/dl. These percentages remained largely unchanged over the course of the study.

As already described, according to the study protocol, therapy adjustments were only allowed in the study from LDL-C values > 130 mg/dl. However, against the background of the long treatment duration of about 5 years, this procedure corresponds neither to the standard of care nor to the guideline recommendations for patients with a (very) high risk of cardiovascular events. Even if it is assumed that a maximally tolerated medicinal therapy is

[4] National Health Care Guideline: Chronic CHD, 5th edition, 2019. https://www.awmf.org/uploads/tx_szleitlinien/nvl-004l_S3_KHK_2019-04.pdf

[5] See data submitted by the pharmaceutical company in the written statement procedure on efficacy endpoints from a post-hoc defined subgroup "LDL-C level < 55 mg/dl at the start of the study".

[6] IQWiG calculation based on the data submitted by the pharmaceutical company on the patients in the REDUCE-IT study who had an LDL-C level above 100 mg/dl in the course of the study: Determination of the percentages not on the basis of the intention-to-treat (ITT) population, but on the basis of those patients who were still under observation at the time of the respective visit.

not indicated for all patients, it is not clear from the documents submitted by the pharmaceutical company to what extent the remaining therapy options (escalation of statin therapy or addition of ezetimibe) were unsuitable or exhausted for the patients. Overall, this leaves great uncertainty as to whether further therapy escalation could or should have been carried out in some of the patients, especially considering the long study duration.

Nevertheless, the REDUCE-IT study is also considered for the benefit assessment according to Section 35a SGB V due to its duration and sample size with approx. 8,200 patients enrolled and the assessment of patient-relevant cardiovascular endpoints.

Extent and probability of the additional benefit

Mortality

There were no differences in overall mortality between the treatment groups.

Morbidity

MACE
The endpoint MACE (major adverse cardiovascular event) is a composite cardiovascular endpoint composed of the individual components "cardiovascular death", "non-fatal myocardial infarction" and "non-fatal stroke".
Regarding the composite endpoint MACE, there is a statistically significant advantage of icosapent ethyl compared to the control arm. The individual components "cardiovascular death", "non-fatal myocardial infarction" and "non-fatal stroke" also show statistically significant advantages of icosapent ethyl.

Hospitalisation
Data on total hospitalisation are not available. The study included the endpoints "hospitalisations due to unstable angina pectoris" and "hospitalisations due to heart failure". As the total hospitalisation is considered a priority, these results are only described additionally. There were statistically significantly fewer "hospitalisations due to unstable angina pectoris" in the icosapent ethyl arm. For the endpoint "hospitalisation due to heart failure", there were no differences between the treatment groups.

Quality of life

Data on health-related quality of life were not assessed in the REDUCE-IT study.

Side effects

There were no differences in therapy discontinuations due to adverse events (AEs) and serious AEs (SAEs) between the treatment groups.
Specific AEs assessed were rhabdomyolysis (PT, AE), haemorrhages (SMQ, AE or SAE) and severe liver toxicity (SMQ, SAEs). Statistically significant haemorrhages (SMQ, AE) occurred more frequently in the icosapent ethyl arm compared to the control arm. For the other endpoints, there were no differences between the treatment groups.

Overall assessment

The benefit assessment of icosapent ethyl for "reducing the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk with elevated triglyceride levels" was based on the randomised, double-blind REDUCE-IT study, which investigated the

administration of icosapent ethyl versus placebo (in each case, in addition to statin and, if required, ezetimibe therapy). Results from the REDUCE- IT study are available on patient-relevant endpoints in the categories of mortality, morbidity and side effects.

There were no differences in overall mortality between the treatment groups.

For morbidity, there is a statistically significant advantage in the icosapent ethyl compared to the control arm for the composite endpoint of MACE. The individual components "cardiovascular death", "non-fatal myocardial infarction" and "non-fatal stroke" also show statistically significant advantages of icosapent ethyl. Data on total hospitalisation are not available.

Data on health-related quality of life were not assessed in the REDUCE-IT study.

With regard to side effects, there were no statistically significant differences between the treatment groups for the endpoints SAEs and discontinuation due to AEs. In detail, the specific AE haemorrhages (SMQ, AE) shows a disadvantage of icosapent ethyl.

In the overall assessment, the results show advantages in the morbidity category for icosapent ethyl in combination with statin compared to statin in combination with ezetimibe, if required. However, against the background of the existing uncertainties, which relate in particular to the lack of therapy adjustment options during the course of the study, it is not possible to conclusively assess the extent of the effects. The lack of possibility to adjust therapy even for LDL-C levels < 130 mg/dl, also against the background of the long treatment duration of about 5 years, corresponds neither to the standard of care nor to the guideline recommendations for patients with a (very) high risk of cardiovascular events. This applies, for example, to the patients who had an LDL-C level > 100 mg/dl during the course of the study (approx. 19% in the icosapent ethyl arm and approx. 26% in the control arm).

In addition, there are further uncertainties regarding the magnitude of the effects due to the use of mineral oil as a placebo in addition to therapy with statins and, if required, ezetimibe. The European Medicines Agency (EMA) has discussed that mineral oil may not be completely inert[7]. For example, substance-specific effects and indirect effects of the mineral oil could lead to a reduced uptake of medicinal products such as statins and influence lipids, lipoproteins and inflammation markers. In this case, according to the EPAR, the effects of icosapent ethyl compared to mineral oil may be overestimated. Ultimately, it remains unclear whether and to what extent the use of mineral oil as a placebo leads to an overestimation of the effect of icosapent ethyl on the endpoint MACE, but this cannot be completely ruled out either.

In summary, the uncertainties described in the REDUCE-IT study mean that the extent of the only minor positive effects of icosapent ethyl is questioned and cannot be conclusively assessed. It remains questionable whether and to what extent the positive effects of icosapent ethyl shown in the study could have been demonstrated if an adjustment of the therapy had especially been allowed to take place during the approximately 5-year treatment period.

Against this background, the G-BA states that an additional benefit of icosapent ethyl in combination with statin compared to the appropriate comparator therapy according to doctor's instructions, taking into account statins and cholesterol absorption inhibitors, is not proven.

[7] European Medicines Agency. Vazkepa; assessment report, 2021. https://www.ema.europa.eu/en/documents/assessment-report/vazkepa-epar-public-assessment-report_en.pdf [accessed: 09.02.2022]

2.1.4 Summary of the assessment

In the present benefit assessment of the new medicinal product Vazkepa with the active ingredient icosapent ethyl, the therapeutic indication assessed here is "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".

The appropriate comparator therapy determined by the G-BA is: "therapy according to doctor's instructions, taking into account statins and cholesterol absorption inhibitors".

For the benefit assessment of icosapent ethyl, the pharmaceutical company uses the randomised, double-blind REDUCE-IT study, in which the administration of icosapent ethyl is investigated in comparison to placebo (in each case, in addition to a therapy consisting of statin and, if required, ezetimibe). The study is also considered for the benefit assessment due to its duration and sample size with approx. 8,200 patients enrolled and the assessment of patient-relevant cardiovascular endpoints.

There were no differences in overall mortality between the treatment groups.

For morbidity, there is a statistically significant advantage in the icosapent ethyl compared to the control arm for the composite endpoint of MACE. The individual components "cardiovascular death", "non-fatal myocardial infarction" and "non-fatal stroke" also show statistically significant advantages of icosapent ethyl. Data on total hospitalisation are not available.

Data on health-related quality of life were not assessed in the REDUCE-IT study.

With regard to side effects, there were no statistically significant differences between the treatment groups for the endpoints SAEs and discontinuation due to AEs. In detail, the specific AE haemorrhages (SMQ, AE) shows a disadvantage of icosapent ethyl.

There are uncertainties in the study, particularly regarding the lack of therapy adjustment options during the course of the study. In addition, further uncertainties arise due to the use of mineral oil as a placebo. In summary, the uncertainties lead to the fact that the extent of the only minor positive effects of icosapent ethyl is questioned and cannot be assessed conclusively.

Against this background, the G-BA states that an additional benefit of icosapent ethyl in combination with statin compared to the appropriate comparator therapy according to doctor's instructions, taking into account statins and cholesterol absorption inhibitors, is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance.

The stated range of approx. 844,000 to 878,000 patients is subject to uncertainties.

The data are based on the pharmaceutical company's derivations in the dossier. For the derivation, the pharmaceutical company uses an analysis of longitudinal insurance data of about 4 million statutorily insured persons from 2010 to 2019 and determines the percentage of patients in the target population from this. However, this analysis is fraught with uncertainties because, on the one hand, only subjects with documented elevated triglyceride levels were included in this analysis. As there were no documented triglyceride levels for about 56% of the patients, this approach potentially leads to an underestimation. On the other, the analysis is not restricted to subjects treated with statins. In addition, there are uncertainties regarding the specific operationalisation of cardiovascular disease or diabetes mellitus.

2.3 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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2022).

For the cost representation only the dosages of the general case are considered. Patient-individual dose adjustments, e.g., because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs. The costs of a possibly necessary titration phase have not been presented since the lipid-lowering therapy is a continuous long-term therapy and the titration is patient-individual. Adherence to a low-fat diet is required.

Medicinal product to be assessed: Icosapent ethyl

The recommended dosage of icosapent ethyl is 2 capsules with 998 mg active ingredient each, 2 x daily, according to the product information.

Since a statin therapy is to be assumed in the present therapeutic indication, a simvastatin therapy in a dosage range of approximately 20 to 80 mg daily is used as an example for the cost calculation. The individual dosage may deviate from this.

Appropriate comparator therapy

From the substance class of statins (HMG-CoA reductase inhibitors), the following active ingredients are available to reduce the risk of cardiovascular events in adults treated with statins who have a high cardiovascular risk and elevated triglyceride levels (≥ 150 mg/dl) as well as proven cardiovascular disease or diabetes and at least one other cardiovascular risk factor: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. To represent the statin therapy, simvastatin in a dosage range of approximately 20 mg to 80 mg was considered as example.

Another lipid-lowering therapy available is the cholesterol absorption inhibitor ezetimibe, which is administered at a daily dose of 10 mg per day.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Icosapent ethyl	continuously, 2 x daily	365	1	365
Simvastatin	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Monotherapy				
Simvastatin	continuously, 1 x daily	365	1	365
Combination therapy				
Simvastatin	continuously, 1 x daily	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365

Consumption:

Designation of the therapy	Dosage	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Icosapent ethyl	1,996 mg	3,992 mg	4 x 998 mg	365	1,460 x 998 mg
Simvastatin	20 mg - 80 mg	20 mg - 80 mg	1 x 20 mg - 1 x 80 mg	365	365 x 20 mg - 365 x 80 mg

Appropriate comparator therapy					
Monotherapy					
Simvastatin	20 mg - 80 mg	20 mg - 80 mg	1 x 20 mg - 1 x 80 mg	365	365 x 20 mg - 365 x 80 mg
Combination therapy					
Simvastatin	20 mg - 80 mg	20 mg - 80 mg	1 x 20 mg - 1 x 80 mg	365	365 x 20 mg - 365 x 80 mg
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both based on the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of usage. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Icosapent ethyl 998 mg	120 SC	€ 269.20	€ 1.77	€ 14.28	€ 253.15
Simvastatin[8] 20 mg	100 FCT	€ 16.91	€ 1.77	€ 0.45	€ 14.69
Simvastatin[8] 80 mg	100 FCT	€ 30.42	€ 1.77	€ 1.51	€ 27.14
Appropriate comparator therapy					
Ezetimibe[8] 10 mg	100 TAB	€ 45.67	€ 1.77	€ 2.72	€ 41.18
Simvastatin[8] 20 mg	100 FCT	€ 16.91	€ 1.77	€ 0.45	€ 14.69
Simvastatin[8] 40 mg	100 FCT	€ 21.67	€ 1.77	€ 0.82	€ 19.08
Simvastatin[8] 80 mg	100 FCT	€ 30.42	€ 1.77	€ 1.51	€ 27.14
Ezetimibe 10 mg/ Simvastatin 80 mg[8]	100 TAB	€ 75.12	€ 1.77	€ 5.05	€ 68.30
Abbreviations: FCT = film-coated tablets, TAB = tablets, SC = soft capsules					

[8] Fixed reimbursement rate

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 7 September 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 27 August 2021, the pharmaceutical company submitted a dossier for the benefit assessment of icosapent ethyl to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 August 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient icosapent ethyl.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 December 2021. The deadline for submitting written statements was 22 December 2021.

The oral hearing was held on 10 January 2022.

By letter dated 11 January 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 28 January 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI

umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 8 February 2022, and the proposed resolution was approved.

At its session on 17 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	7 September 2021	Determination of the appropriate comparator therapy
Working group Section 35a	4 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	10 January 2022 11 January 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 January 2022 1 February 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	8 February 2022	Concluding discussion of the draft resolution
Plenum	17 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 17 February 2022

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

Prof. Hecken