Justification

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Bempedoic acid (Primary hypercholesterolaemia or mixed dyslipidaemia)

of 15 April 2021

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 submission 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.

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th 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 submission on the market of the combination of active ingredient bempedoic acid 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 November 2020. 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 29 October 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 February 2021 on the website of the G-BA (www.g-ba.de), 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 bempedoic acid 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, and the statements submitted in the written statement and oral hearing procedure. 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 bempedoic acid.

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 bempedoic acid (Nilemdo) in accordance with the product information

Nilemdo is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, in addition to diet:

- in combination with a statin or a statin together with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated statin dose (see sections 4.2, 4.3 and 4.4)

  or

- alone or in combination with other lipid-lowering agent therapies in patients who are statin-intolerant or for whom a statin is contraindicated.

Therapeutic indication of the resolution (resolution from the 15/04/2021):

see therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who have not yet exhausted medicinal and dietary options to reduce lipid levels

Appropriate comparator therapy for bempedoic acid:

- Maximum tolerated medicinal therapy according to the doctor's instructions, taking into account statins, cholesterol absorption inhibitors and anion exchangers

b) Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who have already exhausted medicinal (except evolocumab) and dietary optionsto reduce lipid levels

Appropriate comparator therapy for bempedoic acid:

- Evolocumab[2] or LDL apheresis (as a "ultima ratio" for therapy-refractory courses), if necessary with concomitant medicinal-based lipid-lowering therapy.

[1] General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.
[2] The requirements regarding the prescription restriction of the Pharmaceutical Directive (AM-RL) Annex III must be considered.

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. 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 patient-relevant benefit has already been determined by the Federal Joint Committee 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. For the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia the following authorised medicines in the therapeutic indication come into question: HMG-CoA reductase inhibitors (statins), fibrates, anion exchangers - resins (bile acid - binder), ezetimibe as a cholesterol absorption and the PCSK9 inhibitors evolocumab and alirocumab[3]. Medicinal product containing nicotinic acid (derivatives) are no longer approved in Europe.

on 2. According to the G-BA guideline on examination and treatment methods for statutory health care, LDL apheresis is a service that can be performed within the framework of the statutory health insurance (SHI) and is therefore a possible non-medicinal treatment option within the framework of the appropriate comparator therapy.

on 3. The following resolutions of the G-BA are available for this therapeutic indication.

- The G-BA has made the following resolutions on the benefit assessment for the therapeutic indication to be considered in this procedure:
  - Evolocumab (resolution of 9 March 2016 additional benefit not proven; resolution of 6 September 2018 - benefit assessment pursuant to Section 14 VerfO, additional benefit not proven),
  - Alirocumab (resolution of 4 May 2016, additional benefit not proven; resolution of 2 May 2019 - benefit assessment pursuant to Section 14 VerfO, additional benefit not proven),
  - Lomitapide (resolution of 27 November 2015, additional benefit not proven).

[3] Alirocumab has not been available on the German market since 1 September 2019.

- The provisions of the Pharmaceutical Directive (AM-RL) Annex III concerning Prescription restrictions of lipid-lowering agents in this indication must be observed. According to Annex III, No. 35 there is a prescription restriction for prescription lipid-lowering agents,
  - except for manifested vascular disease (CHD, cerebrovascular manifestation, PAOD)
  - except in the case of high cardiovascular risk (over 20% event rate/ 10 years based on the available risk calculators)
  - except in patients with genetically confirmed familial chylomicronaemia syndrome and a high risk of pancreatitis.

- Furthermore, according to Annex III No. 35a and 35b, there are prescription restrictions for the prescription active ingredient evolocumab and alirocumab[3] in the present indication. Accordingly, evolocumab and alirocumab[3] cannot be prescribed as long as they are associated with additional costs compared to therapy with other lipid-lowering agents (statins, fibrates, anion exchangers, cholesterol absorption inhibitors). This does not apply to patients:
  - with familial, homozygous hypercholesterolaemia, in whom medicinal and dietary options for lipid-lowering have been exhausted (see Annex III 35a. evolocumab) or
  - with heterozygous familial or non-familial hypercholesterolaemia or mixed dyslipidaemia with treatment-refractory courses, in which the LDL-C is basically despite a maximum dietary and medicinal lipid-lowering therapy (statins and / or other lipid-lowering agents with statin contraindication) documented over a period of 12 months the value cannot be reduced sufficiently, and it is therefore assumed that the indication to perform LDL apheresis exists. Only patients with confirmed vascular disease (CHD, cerebrovascular manifestation, PAOD) as well as other risk factors for cardiovascular events (e.g. diabetes mellitus, kidney function GFR below 60 ml/min) and patients with confirmed familial heterozygous hypercholesterolaemia, taking into account the Overall risk of familial burden. *(see Annex III 35a evolocumab and 35b alirocumab).*

- Therapy information (AM-RL Annex IV): the therapy information for the active ingredient ezetimibe (G-BA resolution of 17 December 2009) was repealed by a resolution of 22 November 2018. An IQWiG report on the benefit assessment of ezetimibe (Rapid Report Version 2.0) from 3.09.2019 is available.

- The guideline of the Federal Joint Committee on examination and treatment methods for statutory medical care regulates in Annex I: Recognised examination or treatment methods - the requirements for the implementation and billing of apheresis within the framework of statutory medical care. According to this guideline, highly effective standard medication therapies are generally available in contract medical care, so that apheresis should only be used in exceptional cases as the "ultima ratio" in the case of therapy-refractory courses. For example, LDL apheresis can only be carried out in homozygous patients with familial hypercholesterolaemia or in patients with severe hypercholesterolaemia in whom the LDL cholesterol cannot be sufficiently reduced with a maximum dietary and medicinal therapy documented for over twelve months. The overall risk profile of the patient should be in the foreground when considering the indication.

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.

For the treatment of primary hypercholesterolaemia or mixed dyslipidaemia in addition to dietary therapy, medicinal and non-medicinal therapies to reduce LDL cholesterol (LDL-C) are used according to the therapy recommendations from relevant guidelines.

In all guidelines relevant in the therapeutic indication, medicinal product therapy with statins is named as the standard in the care of patients with hypercholesterolaemia. The influence of statins on cardiovascular events has been investigated in several randomised, controlled trials. Differences in benefit between the individual statins with regard to the present indication have not been proven.

If the maximum tolerated dose of the statins does not lower the LDLC values sufficiently, adjunctive therapy with ezetimibe is recommended. For ezetimibe, the IMPROVE-IT study[4] presented a cardiovascular endpoint study that showed statistically significant differences in the primary morbidity endpoint compared to therapy with simvastatin alone. For the other lipid-lowering agents (fibrates or anion exchangers), the available evidence with regard to the influence on patient-relevant endpoints is limited. Against this background, fibrates in particular are not determined as part of the appropriate comparator therapy.

Based on the marketing authorisation, anion exchangers (colesevelam, cholestyramine) can be used in addition to statins and ezitimibe. Otherwise, non-statin lipid-lowering agents are usually only indicated as monotherapy for patients for whom statin therapy is not an option due to contraindications or therapy-limiting side effects. Ezetimibe monotherapy is recommended if there is a contraindication or intolerance to statins.

The maximum tolerated medicinal therapy can also include the combination of different medicinal classes; It is assumed that comparable therapy regimes are used in the intervention arm and in the comparison arm (fair comparison of the lipid-lowering agents used, dosages, etc.)

If the desired lowering of LDL cholesterol cannot be achieved with a maximally tolerated lipid-lowering agents therapy, according to the guideline recommendation, LDL apheresis, possibly in addition to lipid-lowering therapy, represents the next option of therapy escalation. Even if the evidence base for LDL apheresis is limited, this represents an established and recognised method in the care context. The regulations of the G-BA guideline on examination and treatment methods in SHI-accredited medical care apply to LDL apheresis

The PCSK-9 inhibitor evolocumab is an alternative to LDL apheresis. The PCSK-9 inhibitor alirocumab has not been available in Germany since September 2019. Evolocumab can thus - in compliance with the Ordinance - restrictions in Annex III - as another option for patients for whom the other lipid-lowering therapy options have been exhausted, are applied.

The marketing authorisations and product information for the medicinal product of the appropriate comparator therapy must be observed.

In patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, who have not yet exhausted medicinal and dietary options to reduce lipid levels prior to enrolment in the study, the continuation of an inadequate therapy (including the dosage) during the course of the study, cannot be considered as an adaquate implementation of the appropriate comparator therapy.

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

[4] Cannon CP, Blazing MA, Giuliano RP, et al: Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372: 2387-2397.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of bempedoic acid is assessed as follows:

a) Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who have not yet exhausted medicinal and dietary options to reduce lipid levels

An additional benefit is not proven.

b) Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia who have already exhausted medicinal (except evolocumab) and dietary options to reduce lipid levels

An additional benefit is not proven.

Justification:

Patient group a)

The two double-blind randomised controlled studies (RCT) CLEAR HARMONY and CLEAR WISDOM are available to assess the additional benefit of bempedoic acid for the treatment of primary hypercholesterolaemia or mixed dyslipidaemia as an addition to diet. In addition, the pharmaceutical company presents the RCT CLEAR SERENITY as a supplement, which, however, he does not present for the derivation of an additional benefit, but only as support.

CLEAR HARMONY, CLEAR WISDOM studies

In the studies CLEAR HARMONY and CLEAR WISDOM were a total of 2230 or 779 adult patients included with high cardiovascular risk, who exhibited an insufficiently controlled LDL-C value in the range ≥ 70 / mg dl with their existing lipid-lowering therapy. A high cardiovascular risk was defined as the occurrence of an atherosclerotic cardiovascular disease (ASCVD) or a heterozygous familial hypercholesterolemia (HeFH). Patients with ASCVD had to have a documented history of coronary heart disease (including myocardial infarction, unstable angina pectoris) or other risk equivalents (including ischemic stroke). The proportion of patients with ASCVD in the CLEAR HARMONY and CLEAR WISDOM study was 98% and 95%, respectively. HeFH was only found in a small proportion of patients (less than 10 %).

As part of a 52-week treatment phase, the participants involved in the study received either bempedoic acid or placebo in a ratio of 2 to 1 once a day, in each case in addition to their existing lipid-lowering background therapy. In addition, according to the study protocol, the background therapy had to be carried out as a stable, maximum tolerated doses therapy, and as such it should already have been administered in stable manner before the screening for at least four weeks. Furtheremore this stable background therapy should be continued during treatment phase without adjustments. Only on condition of exceeding pre-defined LDL-C thresholds (> 170 mg / dl and ≥ 25% from baseline), it was only allowed to adapt the background therapy in the sense of a rescue therapy, but exclusively starting from week 24.

In the CLEAR HARMONY study, safety endpoints were recorded as the primary endpoint, such as adverse events (AEs) and clinical safety laboratory parameters, among others. In the CLEAR WISDOM study, the primary endpoint was the change in LDL-C at week 12. Other endpoints in both studies included mortality, cardiovascular events, and in the CLEAR WISDOM UE study.

Comparator therapy

In the included study participants are patients whose LDL-C levels were already insufficiently controlled under the existing maximally tolerated lipid-lowering therapy prior to study enrolment. As an appropriate comparator therapy in this patient group, the G-BA determined

a maximum tolerated medicinal therapy according to the doctor's instructions, taking into account statins, cholesterol absorption inhibitors and anion exchangers.

The existing maximally tolerated lipid-lowering therapy, which had to be stable for at least 4 weeks prior to screening, included a maximally tolerated statin in both studies either alone or in combination with other lipid-lowering agents. There is no documented assessment by the treating physicians of the maximum tolerated lipid-lowering therapy. In any case, the maximum tolerated lipid-lowering therapy is not to be equated with the fact that all therapy options had already been exhausted at the start of the study. This is because at the start of the study, mainly statins had been administered without other lipid-modifying drugs; moreover, other lipid-lowering drugs such as cholesterol resorption inhibitors, anion exchangers were hardly used alone or in combination with statins. Only when defined LDL-C threshold values were exceeded from week 24 onwards, and thus only when the LDL-C values, which were already inadequately controlled at the start of the study, deteriorated further, was it possible to change the background therapy in the sense of a rescue therapy by adjusting the dose or adding new active ingredients. Thus, after randomisation in the comparator arm, only 10% of patients in the CLEAR HARMONY trial and only 9% in the CLEAR WISDOM trial received rescue therapy. Statins were used in the majority of cases. An adjustment through additional administration of cholesterol resorption inhibitors or anion exchangers was only carried out in < 1% of the patients. Therefore, the vast majority of patients in the placebo arm continued their inadequate lipid-lowering therapy. In addition, the results on the time course of the mean LDL-C value confirm that hardly any further lipid-lowering medication measures were taken in the comparator arm during the studies.

For an adequate implementation of the appropriate comparator therapy, it would have been necessary for the patients in the comparator arm, who did not show sufficient control of the LCL-C value with their existing maximally tolerated lipid-lowering therapy at study enrolment, to have received an escalation of their lipid-lowering therapy (dose adjustments, administration of an additional lipid-lowering drug, change in the therapy regime). This assumes that additional necessary adjustments of the insufficient lipid-lowering therapy would have to be allowed over the entire course of the study. A therapy escalation at the start of the study or the possibility of an adjustment of therapy over the entire course of the study were not provided for in the submitted studies in the comparator arm.

In summary, the stable background therapy carried out in the studies does not appear appropriate for a fair comparison of bempedoic acid with the appropriate comparator therapy, especially against the background of the high cardiovascular risk in the included patients with an insufficiently adjusted LCL-C value. An additional benefit is not proven.

CLEAR SERENITY Study

A total of 345 adult patients were included in the CLEAR SERENITY study presented by the pharmaceutical company. The prerequisite for participation was that the patients either had a history of lipid-modifying therapy as part of primary prevention, or needed secondary prevention due to cardiovascular events in their history, and / or had HeFH. In addition, patients had to have an LDL-C level of ≥ 130 mg/dl (primary prevention) or ≥ 100 mg/dl (secondary prevention) and statin intolerance. Statin intolerance was defined as intolerance due to AE of two or more statins (one statin at low dose). Therapy with very low-dose statins was allowed. At baseline, 8% of patients received statins.

During a 24 week treatment period, patients received bempedoic acid or placebo in a ratio of 2 to 1, in each case in addition to existing lipid-lowering therapy, which had to be stable in terms of the substances administered and their doses for at least 4 weeks before screening. At baseline, 58% of the study participants were not receiving lipid-lowering therapy. Due to the fact that almost all patients had only received statins and no (additional) other lipid-lowering therapy as previous therapy, the available therapy options are to be considered as not yet exhausted at baseline.

The primary endpoint was the change in LDL-C level at week 12.

Comparator therapy

According to the study protocol, the lipid-lowering therapy could only be adjusted from week 4 onwards if a triglyceride threshold > 1000 mg/dl was exceeded in the sense of a deterioration compared to the start of the study. Therapy adjustments in the course of the study that were based on the LDL-C values were not planned.

In view of the LDL-C value, which was already insufficiently controlled at the start of the study, a need for additional escalation of the existing lipid-lowering therapy, particularly in the comparison arm, can be assumed for the included patients. As described above, however, a therapy escalation of the existing LDL-C-lowering therapy was not planned in the study and was not carried out. Against this background, the appropriate comparator therapy determined by the G-BA is not to be regarded as guaranteed in the study.

Furthermore, the study duration of 24 weeks is too short to adequately depict long-term effects of long-term treatment with bempedoic acid in patients in this population who are dependent on long-term therapy.

In summary, the supplementary study presented by the pharmaceutical company is not suitable for evaluating a comparison of bempedoic acid versus the appropriate comparator therapy. Furthermore, the duration of the study is not suitable for an assessment of long-term effects of bempedoic acid.An additional benefit is therefore not proven. An additional benefit is not proven.

Patient group b)

For the assessment of the additional benefit of bempedoic acid for the treatment of primary hypercholesterolaemia or mixed dyslipidaemia in addition to diet, no data were presented compared to the appropriate comparator therapy. Thus, the additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerts the benefit assessment of the new medicinal product Nustendi with active ingredient bempedoic acid.

Bempedoic acid is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an addition to diet:

- in combination with a statin or a statin together with other lipid-lowering therapies in patients who do not achieve LDL-C goals with the maximum tolerated statin dose

or

- alone or in combination with other lipid-lowering agent therapies in patients who are statin-intolerant or for whom a statin is contraindicated.

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adults with primary hypercholesterolaemia or mixed dyslipidaemia who have not yet exhausted medicinal and dietary options to reduce lipid levels

and

b) Adults with primary hypercholesterolaemia or mixed dyslipidaemia who have already exhausted medicinal (except evolocumab) and dietary optionsto reduce lipid levels.

<u>About patient group a)</u>

As appropriate comparator therapy was the folloging determined: a maximum tolerated medicinal therapy according to the doctor's instructions taking into account statins, cholesterin resorptions inhibitors and anion exchangers.

For the benefit assessment, the studies CLEAR HARMONY, CLEAR WISDOM with a similar design were submitted. The study investigated the administration of bempedoic acid versus placebo, in each case in addition to a maximally tolerated lipid-lowering therapy that the patients had already received as stable therapy for at least 4 weeks before randomisation. During the first 24 weeks of the treatment phase, this background therapy had to remain stable. Only from week 24 onwards adjustments could be made in the event of a deterioration in the LDL-C value, which was already inadequately controlled at the start of the study.

Data on lipid-lowering therapy and mean LDL-C levels over the course of the study suggest that patients in the comparator arm in particular needed therapy escalation and did not receive it. Instead, the vast majority continued their lipid-lowering therapy, which was already inadequate at baseline. Thus, the treatment in the comparator arm does not correspond to the appropriate comparator therapy.

In the supplementary CLEAR SERENITY study in statin-intolerant patients, the appropriate comparator therapy was also not implemented due to the necessary but not implemented therapy escalation.

Thus, an additional benefit is not proven

<u>About patient group b)</u>

As appropriate comparator therapy was the following determined: Evolocumab or LDL apheresis (as the "ultima ratio" in the case of therapy-refractory courses), if necessary with concomitant medicinal-based lipid-lowering therapy.

No data were presented versus the appropriate comparator therapy. An additional benefit 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 (SHI).

Patient group a)

The information provided by the pharmaceutical company in the dossier is generally fraught with uncertainties. On the one hand, only three representatives of the statins group were taken into account. On the other hand, the calculation is based solely on patients with a documented LDL-C value It is unclear to what extent these values can be transferred to the population without documented LDL-C values In addition, the calculation lacks information on patients with statin intolerance, which, according to information from Bempedoic acid, are to be regarded as included in the therapeutic indication.

To determine the number of patients, the G-BA therefore takes into account the underlying information in the previous resolution in the therapeutic indication of hypercholesterolaemia or mixed dyslipidaemia in the corresponding patient groups[5, 6]. However, it cannot be ruled out that, depending on the underlying LDL-C limit value, the total number of patients may be higher.

Patient group b)

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. However, the pharmaceutical company also refers in its calculation to information on patients who receive LDL apheresis with isolated Lp (a) elevation. However, such patients are not included in the approved therapeutic indication of bempedoic acid, so this information was not taken into account. However, it cannot be ruled out that, depending on the underlying LDL-C limit value, the total number of patients may be higher.

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 Nilemdo (active ingredient: bempedoic acid at the following publicly accessible link (last access: 11 March 2021):

https://www.ema.europa.eu/en/documents/product-information/nilemdo-epar-product-information_de.pdf

The prescription restrictions for lipid-lowering agents in accordance with the Pharmaceutical Directive Annex III No. 35 must be taken into account.

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: 15 March 2021).

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. 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.

[5] https://www.g-ba.de/downloads/91-1385-407/2019-05-02_Geltende-Fassung_Alirocumab_D-194_D-409.pdf
[6] https://www.g-ba.de/downloads/91-1385-354/2018-09-06_Geltende-Fassung_Evolocumab_D-345.pdf

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 shown, since the lipid-lowering therapy is a continuous long-term therapy and the titration is patient-specific Adherence to a low-fat diet is required.

Medicinal product to be assessed: Bempedoic acid

The recommended dose of bempedoic acid is 180 mg once daily according to the product information.

Bempedoic acid can be used either in combination with a statin or with a statin and other lipid-lowering therapy principles in patients who do not achieve the LDL-C target values with a maximally tolerated statin therapy, or as monotherapy or in combination with other lipid-lowering therapy principles in patients with a statin intolerance or when statins are contraindicated.

Since a maximum tolerable statin dose is to be assumed in the present therapeutic indication, and according to the product information for bempedoic acid for simultaneous therapy with simvastatin, the daily dose of 20 mg simvastatin or 40 mg simvastatin in patients with severe hypercholesterolaemia and a high risk of cardiovascular complications is not should not be exceeded, is for the cost calculation, the span approximately the dosage range at 20 mg to 40 mg simvastatin daily limited and exemplified.

For the concomitant use of bempedoic acid with other lipid-lowering agents except simvastatin, there are no restrictions in the product information of bempedoic acid except for a staggered intake in combination with bile acid binders. For the combination of bempedoic acid with other lipid-lowering agents besides a statin or in addition to a statin, combinations with ezetimibe and colesevelam were presented as examples for the calculation of the annual treatment costs.

Appropriate comparator therapy

Medicinal lipid-lowering agents therapy

From the substance class of statins (HMG-CoA reductase inhibitors), the following active ingredients are available for the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. The statins are grouped together in the fixed price group of HMG-CoA reductase inhibitors. The calculation was carried out using simvastatin as an example. The dosage range is 5 mg to 80 mg per day. For the representation of a maximally tolerated statin therapy for the appropriate comparator therapy, simvastatin in a dose range of approximately 40 mg to 80 mg was considered as an example.

Then other lipid-lowering agents therapies are available for the two patient groups a) and b) colesevelam, cholestyramine and (anion exchanger) and ezetimibe (cholesterol - resorption - inhibitors) to choose from.

- Anion exchanger For the calculation of the treatment costs, both the costs for colesevelam and cholestyramine were shown The daily dose of cholestyramine for adults is 1 - 4 sachets per day, or a maximum of 6 sachets per day. The recommended daily dose of colesevelam in monotherapy is from 3.75 to 4.375 g (6 - 7 tablets), in combination with ezetimibe, with or without a statin, the recommended 2.5 - 3.75 g (4 - 6 tablets). The presentation of the annual treatment costs takes place in accordance with the appropriate comparative therapy exclusively taking into account the maximum dosage.
- Cholesterol absorption inhibitors: ezetimibe The recommended dosage is 10 mg per day.

For patients in whom the medicinal and dietary options have been exhausted according to patient group b), evolocumab or LDL apheresis is indicated as a "ultima ratio", possibly with accompanying medicinal-based lipid-lowering agents therapy.

A dose of 140 mg evolocumab every 2 weeks or 420 mg every 4 weeks was taken into account when calculating the annual treatment costs under monotherapy with evolocumab or, if applicable, combination therapy with evolocumab with other lipid-lowering agents.

Non-medicinal lipid-lowering agents therapy: LDL apheresis

The attending physician decides on the patient-individual determination of the treatment interval. This usually takes place weekly to every 2 weeks. A concomitant medicinal-based lipid-lowering agents therapy is possible. The annual treatment costs for the implementation of the LDL apheresis consist of a flat rate for material costs (€ 869.20 - € 1,278.23) and the additional flat rate according to the EBM catalogue GOP 13620 (€ 16.58).

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Patient population a)				
Bempedoic acid	continuously, 1 x daily	365	1	365
Simvastatin	continuously, 1 x daily	365	1	365
Colesevelam	continuously, 1-2 times a day	365	1	365
Cholestyramine	continuously, 1-3 times a day	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
Patient population b)				
Bempedoic acid	continuously, 1 x daily	365	1	365
Simvastatin	continuously, 1 x daily	365	1	365
Colesevelam	continuously, 1-2 times a day	365	1	365
Cholestyramine	continuously, 1-3 times a day	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
LDL apheresis	In cycles, every 7 - every 14 days	26.1 – 52.1	1	26.1 – 52.1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Appropriate comparator therapy				
Patient population a)				
Simvastatin	continuously, 1 x daily	365	1	365
Colesevelam	continuously, 1-2 times a day	365	1	365
Cholestyramine	continuously, 1-3 times a day	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
Patient population b)				
evolocumab	In cycles, once every 14 or once every 28 days	13.0 – 26.1	1	13.0 – 26.1
Simvastatin	continuously, 1 x daily	365	1	365
Colesevelam	continuously, 1-2 times a day	365	1	365
Cholestyramine	continuously, 1-3 times a day	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
LDL apheresis	In cycles, every 7 - every 14 days	26.1 – 52.1	1	26.1 – 52.1

Consumption:

Designation of the therapy	Dosage	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Patient population a)					
Bempedoic acid	180 mg	180 mg	1 x 180 mg	365	365 x 180 mg
Simvastatin	20 mg - 40 mg	20 mg 40 mg	1 x 20 mg 1 x 40 mg	365	365 x 20 mg 365 x 40 mg

Designation of the therapy	Dosage	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Colesevelam[7]	2.5 g 3.75 g	2.5 g 3.75 g	4 x 625 mg - 6 x 625 mg	365	1460 x 625 mg 2190 x 625 mg
Cholestyramine	4 g - 8 g	4 g - 24 g	1 x 4 g - 6 x 4 g	365	365 x 4 g - 2190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Patient population b)					
Bempedoic acid	180 mg	180 mg	1 x 180 mg	365	365 x 180 mg
Simvastatin	20 mg - 40 mg	20 mg 40 mg	1 x 20 mg 1 x 40 mg	365	365 x 20 mg 365 x 40 mg
Colesevelam[7]	2.5 g 3.75 g	2.5 g 3.75 g	4 x 625 mg - 6 x 625 mg	365	1460 x 625 mg 2190 x 625 mg
Cholestyramine	4 g - 8 g	4 g – 24 g	1 x 4 g 6 x 4 g	365	365 x 4 g - 2190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
LDL apheresis	Not applicable			26.1 – 52.1	Not applicable
Appropriate comparator therapy					
Patient population a)					
Simvastatin	40 mg - 80 mg	40 mg 80 mg	1 x 40 mg 1 x 80 mg	365	365 x 40 mg 365 x 80 mg
Colesevelam[7]	2.5 g 3.75 g	2.5 g 3.75 g	4 x 625 mg - 6 x 625 mg	365	1460 x 625 mg 2190 x 625 mg
Cholestyramine	4 g - 8 g	4 g - 24 g	1 x 4 g - 6 x 4 g	365	365 x 4 g - 2190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Patient population b)					
evolocumab	140 mg - 420 mg	140 mg - 420 mg	1 x 140 mg 1 x 420 mg	13.0 – 26.1	26.1 x 140 mg 13.0 x 420 mg
Simvastatin	40 mg - 80 mg	40 mg 80 mg	1 x 40 mg 1 x 80 mg	365	365 x 40 mg 365 x 80 mg
Colesevelam[7]	2.5 g 3.75 g	2.5 g 3.75 g	4 x 625 mg - 6 x 625 mg	365	1460 x 625 mg 2190 x 625 mg
Cholestyramine	4 g - 8 g	4 g - 24 g	1 x 4 g - 6 x 4 g	365	365 x 4 g - 2190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg

[7] As a combination therapy: The maximum recommended dose of colesevelam is 6 tablets per day (3.57 g).

Designation of the therapy	Dosage	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
LDL apheresis	Not applicable			26.1 – 52.1	Not applicable

Costs:

Costs of the medicinal product:

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					
Bempedoic acid 180 mg	28 FCT	€ 136.01	€ 1.77	€ 6.92	€ 127.32
Colesevelam 625 mg	180 FCT	€ 205.37	€ 1.77	€ 10.76	€ 192.84
Cholestyramine[8] 4g	400 GSE	€ 53.11	€ 1.77	€ 3.33	€ 48.01
Ezetimibe[8] 10 mg	100 TAB	€ 45.43	€ 1.77	€ 2.72	€ 40.94
Simvastatin[8] 20 mg	100 FCT	€ 16.67	€ 1.77	€ 0.44	€ 14.46
Simvastatin[8] 40 mg	100 FCT	€ 21.43	€ 1.77	€ 0.82	€ 18.84
LDL apheresis	Not applicable				€ 885.78 – € 1,294.81
Appropriate comparator therapy					
Colesevelam 625 mg	180 FCT	€ 205.37	€ 1.77	€ 10.76	€ 192.84
Cholestyramine[8] 4 g	400 GSE	€ 53.11	€ 1.77	€ 3.33	€ 48.01
Evolocumab 140 mg	6 PEN	€ 1,433.63	€ 1.77	€ 78.76	€ 1,353.10
Evolocumab 420 mg	3 ILO	€ 1,551.44	€ 1.77	€ 85.33	€ 1,464.34
Ezetimibe[8] 10 mg	100 TAB	€ 45.43	€ 1.77	€ 2.72	€ 40.94
Simvastatin[8] 20 mg	100 FCT	€ 16.67	€ 1.77	€ 0.44	€ 14.46

[8]fixed reimbursement rate

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
Simvastatin[8] 40 mg	100 FCT	€ 21.43	€ 1.77	€ 0.82	€ 18.84
Simvastatin[8] 80 mg	100 FCT	€ 30.18	€ 1.77	€ 1.51	€ 26.90
LDL apheresis	Not applicable				€ 885.78 – € 1,294.81
Abbreviations: PEN = pre-filled pen; FCT = film-coated tablets; GSE = granules for preparation of an oral suspension; ILO = solution for injection, TAB = tablets.					

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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

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 11 February 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 October 2020, the pharmaceutical company submitted a dossier for the benefit assessment of bempedoic acid to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 30 October 2020 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 bempedoic acid.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 January 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 February 2021. The deadline for submitting the written statements was 22 February 2021.

The oral hearing was held on 9 March 2021.

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 were discussed at the session of the subcommittee on 7 April 2021, and the draft resolution was approved.

At its session on 15 April 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 February 2020	Determination of the appropriate comparator therapy
Working group Section 35a	03 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	09 March 2021	Conduct of the oral hearing
Working group Section 35a	17 March 2021 31 March 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	7 April 2021	Concluding consultation of the draft resolution
Plenum	15 April 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 April 2021

Federal Joint Committee in accordance with Section 91 SGB V The chairman

Prof. Hecken