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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Evinacumab (new therapeutic indication: homozygous familial hypercholesterolaemia, ≥ 5 to < 12 years)

of 4 July 2024

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 active ingredient evinacumab (Evkeeza) was listed for the first time on 1 September 2023 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 11 December 2023, evinacumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 6 January 2024, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5,

Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient evinacumab with the new therapeutic indication

“Evkeeza is indicated as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of **children and adolescents aged 5 to < 12 years** with homozygous familial hypercholesterolaemia (HoFH).“

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 April 2024 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. In addition, an oral hearing was held.

Based on 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, the G-BA decided on the question on whether an additional benefit of rucaparib compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. 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 IQWiG[1] according to the General Methods was not used in the benefit assessment of evinacumab – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

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 Evinacumab (Evkeeza) in accordance with the product information

Evkeeza is indicated as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adults and paediatric patients aged 5 years and older with homozygous familial hypercholesterolaemia (HoFH).

Therapeutic indication of the resolution (resolution of 04.07.2024):

Evkeeza is indicated as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of **children and adolescents aged 5 to < 12 years** with homozygous familial hypercholesterolaemia (HoFH).

[1] General Methods, version 7.0 of 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children and adolescents aged 5 to < 12 years with homozygous familial hypercholesterolaemia for whom dietary and medicinal lipid-lowering options have been exhausted

Appropriate comparator therapy:

- Evolocumab (10 years and older), possibly with concomitant lipid-lowering medicinal therapy, *or*
- LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary with concomitant lipid-lowering medicinal therapy, *or*
- Evolocumab (10 years and older) and LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary with concomitant lipid-lowering medicinal therapy

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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 G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to evinacumab, atorvastatin (10 years and older), lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin are approved as HMG-CoA reductase inhibitors (statins), cholestyramine as anion exchangers, ezetimibe as a cholesterol absorption inhibitor and evolocumab as a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor (10 years and older) for the treatment of homozygous familial hypercholesterolaemia in adolescents aged 12 and older and adults. Gemfibrozil is approved as a fibrate for the treatment of primary hypercholesterolaemia when a statin is contraindicated or not tolerated.

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 G-BA resolutions are available for this therapeutic indication in adolescents aged 12 years and older:

- Resolutions of the G-BA on the early benefit assessment (Annex XII to the Pharmaceuticals Directive):
  - evolocumab (children and adolescents aged between 10 and 11 years with homozygous hypercholesterolaemia: resolution of 16 June 2022)
- The provisions of the Pharmaceuticals 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 existing vascular disease (CHD, cerebrovascular manifestation, PAD)
  - 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, there is a prescription restriction for evolocumab in the present indication. Accordingly, evolocumab cannot be prescribed as long as it is associated with additional costs compared to a 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, or
- with heterozygous familial or non-familial hypercholesterolaemia or mixed dyslipidaemia with treatment-refractory courses, in which the LDL-C value basically, despite a maximum dietary and medicinal lipid-lowering therapy (statins and/or other lipid-lowering agents with statin contraindication) documented over 12 months, 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, PAD) as well as other risk factors for cardiovascular events (e.g. diabetes mellitus, renal function GFR below 60 ml/min) and patients with confirmed familial heterozygous hypercholesterolaemia, taking into account the overall risk of familial burden.

- 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 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 for determining the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

For the treatment of primary hypercholesterolaemia 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 treatment with statins is named as the standard in the care of patients with primary hypercholesterolaemia. The influence of statins on cardiovascular events in adults has been investigated in several randomised, controlled studies. 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 LDL-C values sufficiently, adjunctive therapy with ezetimibe is recommended. For ezetimibe, the

IMPROVE-IT[2] study presented a cardiovascular endpoint study in adults that showed statistically significant differences in the primary morbidity endpoint compared to therapy with simvastatin alone. For anion exchangers, the available evidence is comparatively limited with regard to the influence of patient-relevant endpoints.

Based on the marketing authorisation, anion exchangers can be used in addition to statins and ezetimibe. 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. Only cholestyramine can be used as an anion exchanger in children. The fibrate gemfibrozil is approved in the therapeutic indication in question, but has not been sufficiently studied in children and adolescents.

According to the product information, the patient should already receive an optimal regimen for lowering LDL-C before starting treatment with evinacumab, so that a maximum tolerable lipid-lowering therapy, taking into account statins, cholesterol absorption inhibitors and anion exchangers, is assumed in this therapeutic indication. Against this background, it was assumed in this case that evinacumab is only indicated as an add-on therapy for children and adolescents aged 5 to < 12 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal lipid-lowering options have been exhausted.

The maximum tolerated medicinal therapy can also include the combination of different product classes; 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, and the like).

If the desired reduction in LDL cholesterol cannot be achieved with a maximally tolerated conventional lipid-lowering medicinal treatment, according to the guideline recommendation, evolocumab and/or LDL apheresis, possibly in addition to lipid-lowering therapy, represent the next options of therapy escalation.

Evolocumab is an active ingredient for the treatment of subjects in whom dietary and medicinal treatment options for lipid lowering have been exhausted. The G-BA did not identify any additional benefit of evolocumab for children and adolescents aged 10 to 11 years (resolution of 16 June 2022). However, the active ingredient has been included in the recommendations of relevant guidelines. In view of the fact that a pharmacological therapy option is available for this patient group in addition to LDL apheresis, evolocumab is included in the appropriate comparator therapy for patients (10 years and older).

Even if the body of evidence for LDL apheresis is limited, this represents an established and recognised method in the healthcare context. Accordingly, in children and adolescents aged 5 to < 12 years with homozygous familial hypercholesterolaemia for whom dietary and medicinal lipid-lowering options have been exhausted, evolocumab (10 years and older) or LDL apheresis (as an "ultima ratio" for therapy-refractory courses) or evolocumab (10 years and older) and LDL apheresis (as an "ultima ratio" for therapy-refractory courses), in each case with concomitant lipid-lowering medicinal therapy if necessary, is determined as the appropriate comparator therapy.

[2] 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.

The regulations of the G-BA guideline on examination and treatment methods in SHI-accredited medical care apply to LDL apheresis.

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

In patients with homozygous familial hypercholesterolaemia, in whom dietary and medicinal treatment options for lipid lowering have not been exhausted prior to enrolment in the study, the continuation of an inadequate therapy (including the dosage) during the course of the study does not correspond to the implementation of the appropriate comparator therapy if the individually maximally tolerated medicinal therapy has not yet been exhausted.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

Children and adolescents aged 5 to < 12 years with homozygous familial hypercholesterolaemia for whom dietary and medicinal lipid-lowering options have been exhausted

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of evinacumab for the treatment of children and adolescents aged 5 to < 12 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal lipid-lowering options have been exhausted, the pharmaceutical company uses the single-arm study R1500-CL-17100.

The single-arm R1500-CL-17100 study is unsuitable for making statements on the additional benefit of evinacumab compared with the appropriate comparator therapy due to the lack of a comparison.

An additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new medicinal product Evkeeza with the active ingredient evinacumab. Evkeeza was approved under "exceptional circumstances". The therapeutic indication assessed here is as follows: Children and adolescents aged 5 to < 12 years with homozygous familial hypercholesterolaemia (HoFH).

The appropriate comparator therapy determined by the G-BA for children and adolescents aged 5 to < 12 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal lipid-lowering options have been exhausted is: evolocumab (10 years and older) *or* LDL apheresis (as an "ultima ratio" for therapy-refractory courses) *or* evolocumab (10 years

and older) and LDL apheresis (as an "ultima ratio" for therapy-refractory courses), in each case with concomitant lipid-lowering medicinal therapy if necessary.

The pharmaceutical company submits the single-arm R1500-CL-17100 study for the benefit assessment of evinacumab. The study is unsuitable for making statements on the additional benefit of evinacumab compared to the appropriate comparator therapy due to the lack of a comparison.

An additional benefit is therefore 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).

The G-BA bases its resolution on the patient numbers derived by the pharmaceutical company in the dossier. Overall, the patient numbers are subject to uncertainty due to the limited availability of epidemiological data basis.

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 Evkeeza (active ingredient: evinacumab) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 27 May 2024):

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

This medicinal product was approved under “exceptional circumstances”. This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The EMA will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

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 June 2024).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

As it is not always possible to achieve the exact calculated dose per day with the commercially available dosage potencies, in these cases rounding up or down to the next higher or lower

available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics of the Microcensus[3] 2017 were used as a basis (average body weight of a 5-year-old child: 20.8 kg; average body weight of a 10-year-old child: 37.6 kg; average body weight of a 11-year-old child: 42.1 kg).

Medicinal product to be assessed: Evinacumab

According to the product information, the recommended dosage of evinacumab for children aged 5 years and older is 15 mg/kg BW (every four weeks).

In the present therapeutic indication, a maximum tolerable lipid-lowering therapy is assumed, taking into account statins, cholesterol absorption inhibitors, and anion exchangers. For the classification of a maximally tolerated medicinal therapy for the present patient population, the individual tolerability and the doctor's instructions are decisive.

[3] Federal Health Reporting. Average body measurements of the population (2017, 1 year and older), www.gbe-bund.de

Appropriate comparator therapy

According to the product information, evolocumab is approved for homozygous familial hypercholesterolaemia in children aged 10 years and older. The recommended starting dose is 420 mg once monthly. After 12 weeks of treatment, the dose interval can be increased to 420 mg once every two weeks if a clinically relevant response is not achieved. Apheresis patients can start treatment with 420 mg every two weeks to match their apheresis schedule.

Medicinal lipid-lowering therapy

HMG-CoA reductase inhibitors

From the substance class of statins (HMG-CoA reductase inhibitors), the following active ingredients are basically available for the treatment of primary hypercholesterolaemia: atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. They are grouped together in the reference price group of HMG-CoA reductase inhibitors. Rosuvastatin, which is approved for children aged 6 years and older, was used to calculate the annual treatment costs. According to the product information, the recommended dose range is between 5 and 20 mg once daily.

Anion exchanger (cholestyramine)

For adults, the recommended daily dose of cholestyramine is between 4 g - 24 g per day. The daily dose of cholestyramine for children and adolescents is calculated by dividing the product of the child's body weight and the adult dosage (adult daily dose: 4 g – 24 g) by 70 kg.

Cholesterol absorption inhibitor (ezetimibe)

The recommended dosage for adults is 10 mg ezetimibe continuously once daily according to the product information. Section 4.2 of the product information of ezetimibe does not give a dosage recommendation for paediatric patients. The S2k guideline on the diagnosis and therapy of hyperlipidaemia in paediatric patients[4] was used to calculate the annual treatment costs. This refers to 10 mg of ezetimibe per day.

Non-medicinal lipid-lowering therapy: LDL apheresis

For children and adolescents in whom the medicinal and dietary options have been exhausted according to the patient population, LDL apheresis is indicated as an "ultima ratio" with concomitant lipid-lowering medicinal therapy if necessary.

The attending physician decides on the patient-individual determination of the treatment interval. This usually takes place weekly to every 2 weeks. A concomitant lipid-lowering medicinal 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 (€ 17.78).

[4] http://www.aerztenetz-bad-berleburg.de/images/S2k-Leitlinie-Hyperlipidaemien-Kinder-Jugendliche.pdf (last access: 29 May 2024)

Children and adolescents aged 5 to < 12 years with homozygous familial hypercholesterolaemia for whom dietary and medicinal lipid-lowering options have been exhausted

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				
Evinacumab	In cycles, 1 x every 28 days	13.0	1	13.0
Cholestyramine	Continuously, 1 - 3 x daily	365.0	1	365.0
Evolocumab[5]	In cycles, 1 x every 14 days – 1 x monthly	12.0 - 26.1	1	12.0 - 26.1
Ezetimibe	Continuously, 1 x daily	365.0	1	365.0
Rosuvastatin	Continuously, 1 x daily	365.0	1	365.0
LDL apheresis	In cycles, 1 x every 7 - 14 days	26.1 – 52.1	1	26.1 – 52.1
Appropriate comparator therapy				
• Evolocumab (10 years and older), possibly with concomitant lipid-lowering medicinal therapy, *or* • LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary with concomitant lipid-lowering medicinal therapy, *or* • Evolocumab (10 years and older) and LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary with concomitant lipid-lowering medicinal therapy				
Evolocumab[5]	In cycles, 1 x every 14 days – 1 x monthly	12.0 - 26.1	1	12.0 - 26.1
Cholestyramine	Continuously, 1 - 3 x daily	365.0	1	365.0
Ezetimibe	Continuously, 1 x daily	365.0	1	365.0
Rosuvastatin	Continuously, 1 x daily	365.0	1	365.0
LDL apheresis	In cycles, 1 x every 7 - 14 days	26.1 – 52.1	1	26.1 – 52.1

[5] 10 years and older.

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Evinacumab	Children 5 years and older				
	15 mg/kg BW = 312 mg	312 mg	1 x 345 mg = 1 x 2.3 ml	13.0	13.0 x 345 mg
	Children aged 11 years and below				
	15 mg/kg BW = 631.5 mg	631.5 mg	2 x 345 mg = 2 x 2.3 ml	13.0	26.0 x 345 mg
Cholestyramine	Children 5 years and older				
	0.7 g	1.2 g – 7.1 g	2 x 0.7 – 10 x 0.7 g	365.0	730 x 0.7 g – 3,650 x 0.7 g
	Children 10 years and older				
	0.7 g	2.1 g – 12.9 g	3 x 0.7 g – 18 x 0.7 g	365.0	1,095 x 0.7 g – 6,570 x 0.7 g
	Children aged 11 years and below				
	0.7 g	2.4 g – 14.4 g	4 x 0.7 g – 20 x 0.7 g	365.0	1,460 x 0.7 g – 7,300 x 0.7 g
Evolocumab[5]	420 mg	420 mg	1 x 420 mg	12.0 - 26.1	12.0 x 420 mg – 26.1 x 420 mg
Ezetimibe	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Rosuvastatin	5 mg – 20 mg	5 mg – 20 mg	1 x 5 mg – 1 x 20 mg	365.0	365 x 5 mg – 365 x 20 mg
LDL apheresis	Not applicable			26.1 – 52.1	Not applicable
Appropriate comparator therapy					
• Evolocumab (10 years and older), possibly with concomitant lipid-lowering medicinal therapy, *or* • LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary with concomitant lipid-lowering medicinal therapy, *or* • Evolocumab (10 years and older) and LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary with concomitant lipid-lowering medicinal therapy					
Evolocumab[5]	420 mg	420 mg	1 x 420 mg	12.0 - 26.1	12.0 x 420 mg – 26.1 x 420 mg
Cholestyramine	Children 5 years and older				

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	0.7 g	1.2 g – 7.1 g	2 x 0.7 – 10 x 0.7 g	365.0	730.0 x 0.7 g – 3,650 x 0.7 g
	Children 10 years and older				
	0.7 g	2.1 g – 12.9 g	3 x 0.7 g – 18 x 0.7 g	365.0	1,095 x 0.7 g – 6,570 x 0.7 g
	Children aged 11 years and below				
	0.7 g	2.4 g – 14.4 g	4 x 0.7 g – 20 x 0.7 g	365.0	1,460 x 0.7 g – 7,300 x 0.7 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Rosuvastatin	5 mg – 20 mg	5 mg – 20 mg	1 x 5 mg – 1 x 20 mg	365.0	365 x 5 mg – 365 x 20 mg
LDL apheresis	Not applicable			26.1 – 52.1	Not applicable

Costs:

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 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 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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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					
Evinacumab 345 mg (150 mg/ml)	1 CIS	€ 8,590.32	€ 2.00	€ 490.00	€ 8,098.32
Cholestyramine 0.74 g[6]	400 GOS	€ 53.38	€ 2.00	€ 3.33	€ 48.05
Evolocumab 420 mg	3 SFI	€ 1,413.76	€ 2.00	€ 77.65	€ 1,334.11
Ezetimibe 10 mg[6]	100 TAB	€ 29.80	€ 2.00	€ 1.46	€ 26.34
Rosuvastatin 5 mg[6]	100 FCT	€ 14.77	€ 2.00	€ 0.27	€ 12.50
Rosuvastatin 20 mg[6]	100 FCT	€ 22.99	€ 2.00	€ 0.92	€ 20.07
LDL apheresis	Not applicable				€ 886.98 - € 1,296.01
Appropriate comparator therapy					
Evolocumab 420 mg	3 SFI	€ 1,413.76	€ 2.00	€ 77.65	€ 1,334.11
Cholestyramine 0.74 g[6]	400 GOS	€ 53.38	€ 2.00	€ 3.33	€ 48.05
Ezetimibe 10 mg[6]	100 TAB	€ 29.80	€ 2.00	€ 1.46	€ 26.34
Rosuvastatin 5 mg[6]	100 FCT	€ 14.77	€ 2.00	€ 0.27	€ 12.50
Rosuvastatin 20 mg[6]	100 FCT	€ 22.99	€ 2.00	€ 0.92	€ 20.07
LDL apheresis	Not applicable				€ 886.98 - € 1,296.01
Abbreviations: FCT = film-coated tablets, GOS = granules for oral suspension, CIS = concentrate for the preparation of an infusion solution, SFI = solution for injection, POS = powder for oral suspension, TAB = tablets					

LAUER-TAXE® last revised: 15 June 2024

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 need to be taken into account.

[6] Fixed reimbursement rate

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the

resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in

combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which – patient group-related – a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the

designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Children and adolescents aged 5 to < 12 years with homozygous familial hypercholesterolaemia for whom dietary and medicinal lipid-lowering options have been exhausted

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. According to the requirements in the product information, this therapeutic use involves other therapies for lowering the level of low-density lipoprotein cholesterol (LDL-C).

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:
Product information for

- evinacumab (Evkeeza); Evkeeza 150 mg/ml concentrate for solution for infusion; last revised: no data available
- Evolocumab (Repatha); Repatha® 140 mg solution for injection in a pre-filled pen, Repatha® 420 mg solution for injection in a cartridge; last revised: March 2023

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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 November 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place on the basis of the explanations in the product information of Evkeeza. At its session on 6 February 2024, the Subcommittee on Medicinal Products deleted a patient group of the appropriate comparator therapy.

On 6 January 2024, the pharmaceutical company submitted a dossier for the benefit assessment of evinacumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 10 January 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 evinacumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 April 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 April 2024. The deadline for submitting statements was 6 May 2024.

The oral hearing was held on 27 May 2024.

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 25 June 2024, and the proposed resolution was approved.

At its session on 4 July 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 November 2023	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	6 February 2024	Examination of the appropriate comparator therapy: Deletion of a patient group
Working group Section 35a	14 May 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 May 2024	Conduct of the oral hearing

Working group Section 35a	4 June 2024 18 June 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	25 June 2024	Concluding discussion of the draft resolution
Plenum	4 July 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 4 July 2024

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

Prof. Hecken