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 Alirocumab (new therapeutic indication: hypercholesterolaemia, ≥ 8 years to 17 years)

of 6 June 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 alirocumab (Praluent) was listed for the first time on 15 November 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 15 November 2023, alirocumab 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 12 December 2023, 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 alirocumab with the new therapeutic indication "Treatment of heterozygous familial hypercholesterolaemia (HeFH) in paediatric patients 8 to 17 years of age" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 March 2024 on the G-BA website (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 alirocumab 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 alirocumab.

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 Alirocumab (Praluent) in accordance with the product information

Primary hypercholesterolaemia and mixed dyslipidaemia

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, and in paediatric patients 8 years of age and older with heterozygous familial hypercholesterolaemia (HeFH) as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

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

Therapeutic indication of the resolution (resolution of 6 June 2024):

Praluent is indicated in paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia (HeFH) as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

Appropriate comparator therapy for alirocumab:

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

b) Paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

Appropriate comparator therapy for alirocumab:

- Evolocumab (10 years and older) or 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.

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

on 1. In addition to alirocumab, evolocumab, atorvastatin (both above 10 years), lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin as HMG-CoA reductase inhibitors (statins), cholestyramine as an anion exchanger, ezetimibe as a cholesterol absorption inhibitor as well as fenofibrate, bezafibrate und gemfibrozil are approved as fibrates for the treatment of primary hypercholesterolaemia (heterozygous familial) in paediatric patients 8 years of age and older.

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 have been made for this therapeutic indication in paediatric patients 8 years of age and older:

- Resolutions of the G-BA on the early benefit assessment (Annex XII to the Pharmaceuticals Directive):
  - Evolocumab (paediatric patients 10 years of age and older with heterozygous familial hypercholesterolaemia or mixed dyslipidaemia; 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-only 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, there are prescription restrictions for evolocumab, alirocumab and inclisiran in the present indication in accordance with Annex III Nos. 35a, 35b and 35c. Accordingly, these active ingredients cannot be prescribed as long as they are associated with additional costs compared to a therapy with other lipid-lowering agents (statins, 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 (applies only to evolocumab)
  - 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.

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

In all guidelines relevant to the therapeutic indication, medicinal treatment with statins is mentioned as 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.

Evolocumab is also an active ingredient for the treatment of subjects in whom dietary and medicinal treatment options for lipid lowering have been exhausted. In its decision of 16 June 2022, the G-BA found no additional benefit of evolocumab for patients 10 years of age and older with heterozygous familial hypercholesterolaemia. However, the active ingredient has already been included in the recommendations of relevant guidelines. Taking into consideration that a pharmacological therapy option is now available for this patient group in addition to LDL apheresis, evolocumab is included in the appropriate comparator therapy for patients 10 years of age and older.

Fibrates are approved in the therapeutic indication in question, but have not been sufficiently studied in paediatric patients 8 years of age and older.

In summary, in paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia, in whom dietary and medicinal treatment options for lipid lowering have not been exhausted (patient groups a), a maximally tolerated medicinal

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.

therapy according to the doctor's instructions, taking into account statins, cholesterol absorption inhibitors and anion exchangers, is determined as the appropriate comparator therapy.

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 LDL apheresis, possibly in addition to lipid-lowering therapy, represent the next options of therapy escalation.

Even if the evidence base for LDL-apheresis is limited, this represents an established and recognised method in the healthcare context. Accordingly, in paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia, in whom dietary and medicinal treatment options for lipid lowering have been exhausted (patient group b), evolocumab (children 10 years of age and older) or LDL apheresis (as "ultima ratio" for refractory courses), possibly with concomitant lipid-lowering medicinal therapy is determined as the appropriate comparator therapy. 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 heterozygous 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 alirocumab is assessed as follows:

a) <u>Paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted</u>

An additional benefit is not proven.

b) Paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

An additional benefit is not proven.

Justification:

The pharmaceutical company did not identify any relevant studies for the assessment of the additional benefit of alirocumab in comparison with the appropriate comparator therapy for the present questions. The pharmaceutical company also excludes the possibility of an indirect comparison. The dossier only additionally presents the results of the EFC14643 approval study.

The randomised controlled trial EFC14643 enrolled paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia who were inadequately controlled despite statin treatment with or without additional lipid-modifying therapy or in the case of statin intolerance despite treatment with other (non-statin-based) lipid-modifying therapies. The paediatric patients received either alirocumab or placebo for 24 weeks. Administration of alirocumab took place every 2 or every 4 weeks (Q2W and Q4W cohorts), with the 4-weekly administration corresponding to the dosage recommendation in the product information for alirocumab. This was followed by an 80-week open-label treatment phase in which all patients received alirocumab. A total of 8 patients (10%) in the Q4W cohort had statin intolerance. 22 of the 71 patients treated with statins received the maximum tolerable statin dose (31%), with 47 study participants stating "regional practice or local guideline" as the reason why treatment was not intensified. The lipid-modifying therapy existing at the time of enrolment in the study had to have been given at a stable dose for at least 4 weeks before the start of study and was not allowed to be modified during the double-blind treatment phase. Accordingly, dose adjustments, re-initiation or discontinuation of an existing lipid-modifying therapy were not permitted within the study. Evolocumab and LDL apheresis were not administered in the study.

The maximum tolerated medicinal therapy according to doctor's instructions determined as the appropriate comparator therapy for patient group a) is not considered to be implemented due to the fact that the lipid-modifying therapy cannot be adjusted. Since the study did not use the therapy options evolocumab and LDL apheresis, which were defined as the appropriate comparator therapy for patient group b), no comparison with the appropriate comparator therapy is possible for this patient group either.

Thus, the EFC14643 approval study additionally presented by the pharmaceutical company is unsuitable for the present benefit assessment of alirocumab. In summary, the additional benefit of alirocumab compared with the appropriate comparator therapy for patient groups a) and b) is considered not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient alirocumab.

The therapeutic indication assessed here is as follows: Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed

dyslipidaemia, and in paediatric patients 8 years of age and older with heterozygous familial hypercholesterolaemia (HeFH) as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Only patients 8 to 17 years of age are considered here.

In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

b) Paediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

Patient group a)

As appropriate comparator therapy, the G-BA determined a maximum tolerated medicinal therapy according to doctor's instructions, taking into account statins, cholesterol absorption inhibitors and anion exchangers.

The pharmaceutical company did not identify any relevant studies for the assessment of the additional benefit of alirocumab in comparison with the appropriate comparator therapy for the present question. The EFC14643 approval study additionally presented by the pharmaceutical company is unsuitable for the present benefit assessment of alirocumab for patient group a), as there was no possibility to adjust the lipid-modifying therapy within the study and the appropriate comparator therapy was not implemented accordingly. An additional benefit is therefore not proven.

Patient group b)

As appropriate comparator therapy, the G-BA determined evolocumab (10 years of age and older) or LDL apheresis (as the "ultima ratio" in the case of therapy-refractory courses), possibly with concomitant lipid-lowering medicinal therapy.

The pharmaceutical company did not identify any relevant studies for the assessment of the additional benefit of alirocumab in comparison with the appropriate comparator therapy for the present question. The EFC14643 approval study additionally presented by the pharmaceutical company is unsuitable for the present benefit assessment of alirocumab for patient group b), as evolocumab and LDL apheresis were not administered in the study and the appropriate comparator therapy was not implemented accordingly. 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 derivation of patient numbers for the patient groups is subject to uncertainty. According to the specifications of Annex III to the Pharmaceuticals Directive, the SHI target population is limited to high-risk patients. It is unclear how many patients without high risk the pharmaceutical company included in the respective patient count. In addition, uncertainties arise due to, among other things, the lack of restriction to the underlying disease and due to the inadequate consideration of the (non-)exhaustion of dietary and medicinal lipid-lowering options.

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 Praluent (active ingredient: alirocumab) at the following publicly accessible link (last access: 15 March 2024):

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

The prescription restrictions for alirocumab in the Pharmaceuticals Directive Annex III must be taken into account.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 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 comorbidities) 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 dose 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.

Medicinal product to be assessed: Alirocumab

According to the product information, the recommended dosage for paediatric patients 8 years of age and older is 150 mg to 300 mg alirocumab (every four weeks). In paediatric patients 8 years of age and older who require additional LDL-C reduction, the administration of 75 mg to 150 mg (every two weeks) is recommended.

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.

For the combination of alirocumab with other lipid-lowering agents besides a statin or in addition to a statin, the cholesterol absorption inhibitor ezetimibe and the anion exchanger cholestyramine were presented for the calculation of the annual treatment costs.

Appropriate comparator therapy

The dosage of evolocumab is in principle 420 mg per month according to the product information, whereby a 14-day application of 140 mg is possible as an alternative for heterozygous familial hypercholesterolaemia in paediatric patients 10 to 17 years of age.

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. For paediatric patients 8 to 17 years of age, pravastatin is used as an example for the calculation of the annual treatment costs.

Anion exchanger (cholestyramine)

The daily dose of cholestyramine for paediatric patients 8 to 17 years of age 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.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics of the Microcensus[3] 2017 or 2021 were used as a basis (average body weight of a 8-year-old child: 30.0 kg; average body weight of a 10-year-old child: 37.6 kg; average body weight of 17-year-old adolescent: 67.2 kg).

Cholesterol absorption inhibitor (ezetimibe)

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.

3 Federal Health Reporting. Average body measurements of the population (2017 and 2021: both, aged 1 year and 15 years and over), www.gbe-bund.de

4 http://www.aerztenetz-bad-berleburg.de/images/S2k-Leitlinie-Hyperlipidaemien-Kinder-Jugendliche.pdf (last access: 18 April 2024)

Non-medicinal lipid-lowering therapy: LDL apheresis

For paediatric patients in whom the medicinal and dietary options have been exhausted according to patient group b), LDL apheresis is indicated as an "ultima ratio" possibly with concomitant lipid-lowering medicinal therapy.

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).

Treatment period:

a) Paediatric patients **8 to 17 years** of age with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Alirocumab	In cycles, 1 x every 14 or 1 x every 28 days	13.0 – 26.1	1	13.0 – 26.1
Pravastatin	Continuously, 1 x daily	365.0	1	365.0
Cholestyramine	Continuously, 1-3 x daily[5]	365.0	1	365.0
Ezetimibe	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Maximum tolerated medicinal therapy according to the doctor's instructions, taking into account statins, cholesterol absorption inhibitors and anion exchangers				
Pravastatin	Continuously, 1 x daily	365.0	1	365.0
Cholestyramine	Continuously, 1-3 x daily	365.0	1	365.0
Ezetimibe	Continuously,	365.0	1	365.0

5 The product information of cholestyramine does not give any information on the mode of treatment in paediatric patients. The specified interval corresponds to the mode assigned in the product information for adults.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x daily			

b) Paediatric patients **8 to 17 years** of age with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Alirocumab	In cycles, 1 x every 14 or 1 x every 28 days	13.0 – 26.1	1	13.0 – 26.1
Pravastatin	Continuously, 1 x daily	365.0	1	365.0
Cholestyramine	Continuously, 1-3 x daily	365.0	1	365.0
Ezetimibe	Continuously, 1 x daily	365.0	1	365.0
LDL apheresis	In cycles, every 7 – every 14 days	26.1 – 52.1	1	26.1 – 52.1
Appropriate comparator therapy				
Evolocumab (10 years and older) or LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary with concomitant lipid-lowering medicinal therapy				
Evolocumab	In cycles, 1 x every 14 or 1 x every 28 days	13.0 – 26.1	1	13.0 – 26.1
Pravastatin	Continuously, 1 x daily	365.0	1	365.0
Cholestyramine	Continuously, 1-3 x daily	365.0	1	365.0
Ezetimibe	Continuously, 1 x daily	365.0	1	365.0
LDL apheresis	In cycles,	26.1 – 52.1	1	26.1 – 52.1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	every 7 – every 14 days			

Consumption:

a) Paediatric patients **8 to 17 years** of age with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

Designation of the therapy	Dosage	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Alirocumab	75 mg – 150 mg	75 mg – 150 mg	1 x 75 mg - 1 x 150 mg	26.1	26.1 x 75 mg - 26.1 x 150 mg
	or				
	150 mg – 300 mg	150 mg – 300 mg	1 x 150 mg – 2 x 150 mg	13.0	13 x 150 mg – 26 x 150 mg
Pravastatin	Children (8-13 years)				
	10 mg – 20 mg	10 mg – 20 mg	1 x 10 mg – 1 x 20 mg	365.0	365 x 10 mg – 365 x 20 mg
	Adolescents 14 years of age and older				
	10 mg – 40 mg	10 mg – 40 mg	1 x 10 mg – 1 x 40 mg	365.0	365 x 10 mg – 365 x 40 mg
Cholestyramine	Children 8 years of age				
	1.7 g – 3.4 g	1.7 g – 10.3 g	2 x 0.7 g – 15 x 0.7 g[6]	365.0	730 x 0.7 g – 5,475 x 0.7 g
	Adolescents 17 years of age				
	3.8 g – 7.7 g	3.8 g – 23.0 g	1 x 4 g – 6 x 4 g	365.0	365 x 4 g – 2,190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
Appropriate comparator therapy					
Maximum tolerated medicinal therapy according to doctor's instructions, taking into account statins, cholesterol absorption inhibitors and anion exchangers					

[6] 1 g of the granules contains 0.74 g of cholestyramine.

Designation of the therapy	Dosage	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Pravastatin	Children (8-13 years)				
	10 mg – 20 mg	10 mg – 20 mg	1 x 10 mg – 1 x 20 mg	365.0	365 x 10 mg – 365 x 20 mg
	Adolescents 14 years of age and older				
	10 mg – 40 mg	10 mg – 40 mg	1 x 10 mg – 1 x 40 mg	365.0	365 x 10 mg – 365 x 40 mg
Cholestyramine	Children 8 years of age				
	1.7 g – 3.4 g	1.7 g – 10.3 g	2 x 0.7 g – 15 x 0.7 g	365.0	730 x 0.7 g – 5,475 x 0.7 g
	Adolescents 17 years of age				
	3.8 g – 7.7 g	3.8 g – 23.0 g	1 x 4 g – 6 x 4 g	365.0	365 x 4 g – 2,190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg

b) Paediatric patients **8 to 17 years** of age with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

Designation of the therapy	Dosage	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Alirocumab	75 mg – 150 mg	75 mg – 150 mg	1 x 75 mg - 1 x 150 mg	26.1	26.1 x 75 mg - 26.1 x 150 mg
	or				
	150 mg – 300 mg	150 mg – 300 mg	1 x 150 mg – 2 x 150 mg	13.0	13 x 150 mg – 26 x 150 mg
Pravastatin	Children (8-13 years)				
	10 mg – 20 mg	10 mg – 20 mg	1 x 10 mg – 1 x 20 mg	365.0	365 x 10 mg – 365 x 20 mg
	Adolescents 14 years of age and older				
	10 mg – 40 mg	10 mg – 40 mg	1 x 10 mg – 1 x 40 mg	365.0	365 x 10 mg – 365 x 40 mg

Designation of the therapy	Dosage	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cholestyramine	Children 8 years of age				
	1.7 g – 3.4 g	1.7 g – 10.3 g	2 x 0.7 g – 15 x 0.7 g[6]	365.0	730 x 0.7 g – 5,475 x 0.7 g
	Adolescents 17 years of age				
	3.8 g – 7.7 g	3.8 g – 23.0 g	1 x 4 g – 6 x 4 g	365.0	365 x 4 g – 2,190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 mg
LDL apheresis	Not applicable			26.1 – 52.1	Not applicable
Appropriate comparator therapy					
Evolocumab (10 years and older) or LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary with concomitant lipid-lowering medicinal therapy					
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
Pravastatin	Children (8-13 years)				
	10 mg – 20 mg	10 mg – 20 mg	1 x 10 mg – 1 x 20 mg	365.0	365 x 10 mg – 365 x 20 mg
	Adolescents 14 years of age and older				
	10 mg – 40 mg	10 mg – 40 mg	1 x 10 mg – 1 x 40 mg	365.0	365 x 10 mg – 365 x 40 mg
Cholestyramine	Children 8 years of age				
	1.7 g – 3.4 g	1.7 g – 10.3 g	2 x 0.7 g – 15 x 0.7 g[6]	365.0	730 x 0.7 g – 5,475 x 0.7 g
	Children 10 years of age				
	2.2 g – 4.3 g	2.2 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
	Adolescents 17 years of age				
	3.8 g – 7.7 g	3.8 g – 23.0 g	1 x 4 g – 6 x 4 g	365.0	365 x 4 g – 2,190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365.0	365 x 10 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					
Alirocumab 75 mg	6 SFI	€ 1,305.87	€ 2.00	€ 0.00	€ 1,303.87
Alirocumab 150 mg	6 SFI	€ 1,305.87	€ 2.00	€ 0.00	€ 1,303.87
Cholestyramine 0.74 g[7]	400 GOS	€ 53.38	€ 2.00	€ 3.33	€ 48.05
Cholestyramine 4 g[7]	100 POS	€ 66.75	€ 2.00	€ 4.38	€ 60.37
Ezetimibe 10 mg[7]	100 TAB	€ 29.80	€ 2.00	€ 1.46	€ 26.34
Pravastatin 10 mg[7]	100 TAB	€ 14.77	€ 2.00	€ 0.27	€ 12.50
Pravastatin 20 mg[7]	100 TAB	€ 16.95	€ 2.00	€ 0.45	€ 14.50
Pravastatin 40 mg[7]	100 TAB	€ 21.71	€ 2.00	€ 0.82	€ 18.89
LDL apheresis	Not applicable				€ 886.98 - € 1,296.01
Appropriate comparator therapy					
Evolocumab 140 mg	6 PEN	€ 1,305.87	€ 2.00	€ 71.67	€ 1,232.20
Evolocumab 420 mg	3 SFI	€ 1,413.76	€ 2.00	€ 77.65	€ 1,334.11
Cholestyramine 0.74 g[7]	400 GOS	€ 53.38	€ 2.00	€ 3.33	€ 48.05
Cholestyramine 4 g[7]	100 POS	€ 66.75	€ 2.00	€ 4.38	€ 60.37
Ezetimibe 10 mg[7]	100 TAB	€ 29.80	€ 2.00	€ 1.46	€ 26.34
Pravastatin 10 mg[7]	100 TAB	€ 14.77	€ 2.00	€ 0.27	€ 12.50
Pravastatin 20 mg[7]	100 TAB	€ 16.95	€ 2.00	€ 0.45	€ 14.50
Pravastatin 40 mg[7]	100 TAB	€ 21.71	€ 2.00	€ 0.82	€ 18.89
LDL apheresis	Not applicable				€ 886.98 - € 1,296.01
Abbreviations: SFI = solution for injection; GOS = granules for oral suspension; POS = powder for oral suspension; TAB = tablets					

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[7] Fixed reimbursement rate

Costs for additionally required SHI services:

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

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

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

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:

a) Paediatric patients aged 8 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not 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. This therapeutic indication concerns other lipid-lowering therapies according to the requirements in the product information.

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

- alirocumab (Praluent); Praluent® 75 mg/ 150 mg/ 300 mg solution for injection in a pre-filled pen, Praluent® 75 mg/ 150 mg solution for injection in a pre-filled syringe; last revised: November 2023
- 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

b) Paediatric patients aged 8 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering 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. This therapeutic indication concerns other lipid-lowering therapies according to the requirements in the product information.

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

- alirocumab (Praluent); Praluent® 75 mg/ 150 mg/ 300 mg solution for injection in a pre-filled pen, Praluent® 75 mg/ 150 mg solution for injection in a pre-filled syringe; last revised: November 2023
- 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 12 December 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 12 December 2023 the pharmaceutical company submitted a dossier for the benefit assessment of alirocumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 14 December 2023 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 alirocumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 March 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2024. The deadline for submitting written statements was 5 April 2024.

The oral hearing was held on 22 April 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 28 May 2024, and the proposed resolution was approved.

At its session on 6 June 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 December 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	16 April 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	22 April 2024	Conduct of the oral hearing
Working group Section 35a	29 April 2024; 14 May 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	28 May 2024	Concluding discussion of the draft resolution
Plenum	6 June 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 June 2024

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

Prof. Hecken