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 Evolocumab (new therapeutic indication: primary hypercholesterolaemia, 10 to 17 years)

of 16 June 2022

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient evolocumab (Repatha) was listed for the first time on 15 September 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 26 November 2021, evolocumab 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, 12.12.2008, p. 7).

On 21 December 2021, i.e. no later than four weeks after the pharmaceutical company has been notified of the authorisation for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time 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 evolocumab with the new therapeutic indication (paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia as well as paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 01 April 2022, 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 evolocumab compared to 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 evolocumab.

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 Evolocumab (Repatha) in accordance with the product information

Hypercholesterolaemia and mixed dyslipidaemia

Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, and in paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia, 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 statin dose or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Homozygous familial hypercholesterolaemia

Repatha is indicated in adults and paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Therapeutic indication of the resolution (resolution of 16 June 2022):

Heterozygous familial hypercholesterolaemia

Repatha is indicated in paediatric patients **aged 10 to 17 years with heterozygous familial hypercholesterolaemia**, as an adjunct to diet:

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

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

Homozygous familial hypercholesterolaemia

Repatha is indicated in paediatric patients aged **10 to 11 years with homozygous familial hypercholesterolaemia** in combination with other lipid-lowering therapies.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) Paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

Appropriate comparator therapy:

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

a2) Paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

Appropriate comparator therapy:

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

b1) Paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

Appropriate comparator therapy:

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

b2) Paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

Appropriate comparator therapy:

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

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the 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.

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

On 1. In addition to evolocumab, atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin as HMG-CoA reductase inhibitors (statins), cholestyramine as an anion exchanger and ezetimibe as a cholesterol absorption inhibitor are approved for the treatment of primary hypercholesterolaemia (heterozygous familial or homozygous familial) in paediatric patients aged 10 years and older. Fibrates are approved in the therapeutic indication, but have not been sufficiently studied in paediatric patients aged 10 years 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 aged 10 years and older:

- Resolutions of the G-BA on the early benefit assessment (Annex XII to the Pharmaceuticals Directive):

  Evolocumab (adolescents 12 years and older with homozygous hypercholesterolaemia: Resolution of 9 March 2016)

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

In all guidelines relevant in the therapeutic indication, medicinal therapy 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.

In summary, in paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia and in paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia, in whom dietary and medicinal options for lipid lowering therapy have not been exhausted (according to patient groups a1 and b1), a maximally tolerated medicinal 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 lowering of LDL cholesterol cannot be achieved with a maximally tolerated lipid-lowering therapy, according to the guideline recommendation, LDL apheresis, possibly in addition to lipid-lowering therapy, represents the next option of therapy escalation. Even if the evidence base for LDL apheresis is limited, this represents an established and recognised method in the healthcare context. Accordingly, in paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia and in paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia, in whom dietary and medicinal options for lipid lowering therapy have been exhausted (according to patient groups a2 and b2), LDL apheresis (as "ultima ratio" in therapy-refractory courses) is determined as the appropriate comparator therapy, if necessary with concomitant medicinal lipid-lowering 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 or homozygous familial hypercholesterolaemia, in whom medicinal and dietary options for lipid-lowering therapy were not exhausted prior to time of 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.

[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.

2.1.3 Extent and probability of the additional benefit

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

a1) Paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

An additional benefit is not proven.

a2) Paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

An additional benefit is not proven.

b1) Paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

An additional benefit is not proven.

b2) Paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

An additional benefit is not proven.

Justification:

a1) Paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

The pharmaceutical company submits the HAUSER-RCT study for the assessment of the additional benefit of evolocumab for the treatment of paediatric patients with heterozygous familial hypercholesterolaemia aged 10 to 17 years, in whom dietary and medicinal options for lipid lowering therapy have not been exhausted.

HAUSER-RCT study

The HAUSER-RCT randomised, controlled, double-blind study investigated the administration of evolocumab versus placebo, each in combination with a low-fat diet and stable lipid-lowering therapy in paediatric patients aged 10 to 17 years with diagnosed heterozygous familial hypercholesterolaemia (HeHF)[3].

For screening, patients had to have an LDL-C value ≥ 130 mg/dl in the fasting state and had to have been treated with an approved, stable dosage of statin, requiring no further intensification at the discretion of the principal investigator, ≥ 4 weeks prior to LDL-C screening. In addition, patients had to follow a low-fat diet and could additionally be treated with other lipid-lowering agents, such as ezetimibe, anion exchangers, omega-3 fatty acids or

[3] Diagnosis based on genetic tests or local diagnostic criteria: Simon-Broome Register Group, Dutch Lipid Clinic Network or Make Early Diagnosis and Prevent Early Death.

niacin, provided that a stable dosage of these were administered ≥ 4 weeks or, in the case of treatment with fibrates, ≥ 6 weeks prior to LDL-C screening.

A total of 158 paediatric patients were enrolled in the HAUSER-RCT study and were randomised in a 2:1 ratio (evolocumab: placebo). Stratification was according to the characteristics of LDL-C level at screening (< 160 mg/dl vs ≥ 160 mg/dl) and age at randomisation (< 14 years and ≥ 14 years).

The treatment in the HAUSER-RCT study took place over 24 weeks. The primary endpoint of the study was the change in LDL-C level by week 24. Other endpoints were assessed in the categories of morbidity and side effects.

Subsequently, all paediatric patients were able to switch to the single-arm, open-label, extension study HAUSER-OLE and receive treatment with evolocumab.

Prior therapy with maximum tolerable statin dose not ensured

According to the marketing authorisation, the prerequisite for the use of evolocumab in the present indication in patients who are eligible for statin therapy is the non-achievement of the LDL-C target values under a maximum tolerable statin dose. For children aged 10 years and older, national and European guidelines recommend an LDL-C level < 135 mg/dl[4,5] or ≤ 130 mg/dl[6].

The HAUSER-RCT study enrolled paediatric patients who were already being treated with atorvastatin, rosuvastatin, pravastatin or simvastatin at the start of the study. For the most part, the dosage of these statins did not correspond to the maximum permissible dose for paediatric patients with HeFH. For example, only one patient was treated with the maximum permitted dose of atorvastatin (80 mg), whereas the majority of patients received only 10 mg or 20 mg of atorvastatin. Although the statin therapy did not require further intensification at the discretion of the principal investigator according to the inclusion criteria, the reasons why intensification of statin therapy was not necessary or not possible despite a mean LDL-C value of 184 mg/dl at the start of the study are not available. Also, any criteria that principal investigators used to exclude intensification of statin therapy are not known. The statin therapy used in the patients before the start of the study can therefore not per se be regarded as the maximum tolerable dosage. The product information and guidelines on the dosages of statins in paediatric patients point out that the dose should be titrated or adjusted according to individual response and tolerability in order to achieve the corresponding target values. Therefore, it is assumed that the approved maximum dose does not necessarily correspond to the maximum tolerated dose. However, without giving reasons, it is not plausible that the approved daily maximum dose for paediatric patients was only reached in exceptional cases. Therefore, for the majority of the paediatric patients enrolled, it is not ensured that they were treated with a maximum tolerable statin dose and that a therapy with evolocumab was indicated at all according to the specifications of the marketing authorisation.

[4] Mach et al. (2019) ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41(1): 111-188. https://dx.doi.org/10.1093/eurheartj/ehz455

[5] German Society of Cardiology - Cardiovascular Research (2019), European Society of Cardiology: Diagnostics and therapy of dyslipidaemias, https://leitlinien.dgk.org/files/19_2019_pocket_leitlinien_dyslipidaemien_korrigiert.pdf [Accessed: 31.01.2022]

[6] Working Group for Paediatric Metabolic Disorders in the German Society of Paediatrics and Adolescent Medicine (2015): S2k guidelines on the diagnosis and treatment of hyperlipidaemia in paediatric patients, http://www.aerztenetz-bad-berleburg.de/images/S2k-Leitlinie-Hyperlipidaemien-Kinder-Jugendliche.pdf [Accessed: 01.02.2022]

Implementation of the appropriate comparator therapy

For paediatric patients with HeHF aged 10 to 17 years who have not exhausted dietary and medicinal options for lipid lowering therapy, the appropriate comparator therapy was defined as a maximally tolerated medicinal therapy according to the doctor's instructions, taking into account statins, cholesterol absorption inhibitors and anion exchangers.

In the HAUSER-RCT study, almost all patients received a statin as part of the lipid-lowering therapy (except for one patient in the control arm with ezetimibe monotherapy). In addition, a small percentage of the study population also received ezetimibe (13%), fish oil (4%), phytosterols (1%) or colesevelam (1%) as part of lipid-lowering therapy.

During the entire course of the study, adjustments or optimisations of the lipid-lowering therapy were planned neither in the intervention nor the control arm. Rather, the therapy in place at the start of the study should be continued unchanged. Adjustments to lipid-lowering therapy were possible if clinically necessary according to the study protocol, but were not carried out in any patient. In addition, the definition of clinical necessity is not clear from the study documents. Therapy adjustments in the sense of a maximally tolerated medicinal therapy, such as the combination of the existing lipid-lowering therapy with an additional lipid-lowering active ingredient, a change of the active ingredient or dose adjustments, were therefore not possible in the HAUSER-RCT study. In addition, the principal investigators in the study were blinded to lipid parameters, among others, from randomisation until 12 weeks after the last treatment with the study medication or termination of the study. However, the LDL-C value in particular is a relevant lipid parameter for therapy control in the present indication, so that a target-value-oriented therapy according to medical guidelines was not possible at all in the HAUSER-RCT study. The lack of therapy adjustment is also reflected in the study results for the percentage change in LDL-C levels: at the start of the study, LDL-C levels were on average 184 mg/dl and these remained almost unchanged in the control arm throughout the course of the study, with a further reduction in LDL-C levels achieved in the intervention arm through the additional administration of evolocumab. The LDL-C values at the start of the study were outside the target range, so that an optimisation of the lipid-lowering therapy would have been indicated in the majority of patients. The continuation of an inadequate therapy (including the dosage) in the course of the study does not correspond to the implementation of the appropriate comparator therapy defined by the G-BA, provided that the individual maximum tolerated drug therapy has not yet been exhausted. For an adequate comparison, however, it would have been necessary to take further measures to reduce LDL-C levels in the control arm during the course of the study, such as dose adjustments or dose escalation, the additional administration of another lipid-lowering agent or even a switch to another lipid-lowering regimen.

Furthermore, the duration of the study is unsuitable for an assessment of long-term effects of evolocumab.

<u>Conclusion</u>

Since, on the one hand, it is not ensured in the HAUSER-RCT study for the majority of the paediatric patients enrolled that they were treated with a maximum tolerable statin dose and that a therapy with evolocumab was indicated at all according to the specifications of the marketing authorisation and, on the other, the appropriate comparator therapy defined by the G-BA, a maximum tolerated drug therapy according to the doctor’s instructions, was not implemented, the study cannot be used for the derivation of the additional benefit. Furthermore, the duration of the study is unsuitable for an assessment of long-term effects of

evolocumab. An additional benefit of evolocumab compared to the appropriate comparator therapy is therefore not proven in this patient group.

a2) Paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

No data were presented for the assessment of the additional benefit of evolocumab for the treatment of paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal options for lipid lowering have not been exhausted.

An additional benefit is not proven.

b1) Paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

The pharmaceutical company additionally presents the single-arm HAUSER-OLE study for the assessment of the additional benefit of evolocumab for the treatment of paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia (HoHF) in whom dietary and medicinal options for lipid lowering have not been exhausted.

However, in line with the assessment of the pharmaceutical company, the single-arm HAUSER-OLE study is not suitable for deriving conclusions on the additional benefit of evolocumab compared to the appropriate comparator therapy due to the lack of comparison.

An additional benefit is not proven.

b2) Paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

No data were presented for the assessment of the additional benefit of evolocumab for the treatment of paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal options for lipid lowering have been exhausted.

An additional benefit is 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 evolocumab (Repatha). The therapeutic indication assessed here is as follows: Paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia and paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia.

In the therapeutic indication to be considered, 4 patient groups were distinguished:

a1) Paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

a2) Paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

b1) Paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have not been exhausted

b2) Paediatric patients aged 10 to 11 years with homozygous familial hypercholesterolaemia in whom dietary and medicinal treatment options for lipid lowering have been exhausted

On patient group a1)

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

The pharmaceutical company presents the randomised, controlled, double-blind HAUSER-RCT study investigating the administration of evolocumab versus placebo, each in combination with a low-fat diet and stable lipid-lowering therapy in paediatric patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia.

However, the study is unsuitable for the benefit assessment because, on the one hand, it is not ensured for the majority of the children and adolescents enrolled that they were treated with a maximum tolerable statin dose and thus, a therapy with evolocumab was indicated at all according to the specifications of the marketing authorisation. On the other, the paediatric patients did not receive any adjustment of their lipid-lowering therapy in the further course of the study, despite increased LDL-C values that were above the target range, so that the appropriate comparator therapy was not implemented. Furthermore, the duration of the study is unsuitable for an assessment of long-term effects of evolocumab.

An additional benefit is not proven.

On patient group a2)

The appropriate comparator therapy determined by the G-BA is: LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary, with concomitant medicinal lipid-lowering therapy.

For the assessment of the additional benefit of evolocumab, no data were presented for this patient group compared to the appropriate comparator therapy.

An additional benefit is not proven.

On patient group b1)

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

For the assessment of the additional benefit of evolocumab, the single-arm HAUSER-OLE study was submitted by the pharmaceutical company. However, in line with the assessment of the

pharmaceutical company, the single-arm HAUSER-OLE study is unsuitable for deriving statements on the additional benefit of evolocumab compared to the appropriate comparator therapy due to the lack of comparison.

An additional benefit is not proven.

On patient group b2)

The appropriate comparator therapy determined by the G-BA is: LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary, with concomitant medicinal lipid-lowering therapy.

For the assessment of the additional benefit of evolocumab, no data were presented for this patient group compared to the appropriate comparator therapy.

An additional benefit is not proven.

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

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

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 the case of HeHF, uncertainties also 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 options for lipid lowering.

In the case of HoHF, the order of magnitude of the patient numbers seems plausible, but there are no data available that allow an allocation of the patients to the two patient groups b1 and b2.

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 Repatha (active ingredient: evolocumab) at the following publicly accessible link (last access: 31 May 2022):

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

The prescription restriction for evolocumab in the Pharmaceuticals Directive Annex III must be taken into account.

2.4 Treatment costs

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

Medicinal product to be assessed: Evolocumab

The dosage of evolocumab is in principle 420 mg per month according to the product information[7], whereby a 14-day application of 140 mg is possible as an alternative for heterozygous familial hypercholesterolaemia in paediatric patients aged 10 to 17 years. For patients with homozygous familial hypercholesterolaemia aged 10 years and older, the dose may be increased up to 420 mg every 14 days.

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 evolocumab 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

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 fixed reimbursement rate group of HMG-CoA reductase inhibitors. For paediatric patients aged 10 to 17 years, simvastatin is used as an example for the calculation of the annual treatment costs. The maximum recommended dose of simvastatin in paediatric patients aged 10 to 17 years is 40 mg per day. The starting dose of simvastatin is 10 mg for paediatric patients with heterozygous familial hypercholesterolaemia. The calculation of the annual treatment costs is based on the dosage range of 10 mg - 40 mg simvastatin for both patient groups (heterozygous and homozygous).

Anion exchanger (cholestyramine)
The daily dose of cholestyramine for paediatric patients aged 10 to 11 or 17 years 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. The average body measurements were applied for dosages depending on body weight or body surface area (BSA) (average height of a 10-year-old child: 1.44 m; average body weight: 37.6 kg, of an 11-year-old child: 1.50 m and 42.1 kg, of a 17-year-old adolescent: 1.74 m and 67.0 kg) (calculation according to Du Bois 1916).[8]

[7] https://www.ema.europa.eu/en/documents/product-information/repatha-epar-product-information_en.pdf (last revised: 05.05.2022).
[8] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Cholesterol absorption inhibitor (ezetimibe)
Section 4:2 of the product information of ezetimibe does not give a dosage recommendation for paediatric patients[9]. The S2k guideline on the diagnosis and therapy of hyperlipidaemia in paediatric patients[10] 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 paediatric patients in whom the medicinal and dietary options have been exhausted according to patient group a2) and b2), LDL apheresis is indicated as an "ultima ratio" possibly with accompanying medicinal lipid-lowering 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 medicinal-based lipid-lowering agents therapy is possible. The annual treatment costs for the implementation of the LDL apheresis consist of a flat rate for material costs (€ 869.20 - € 1,278.23) and the additional flat rate according to the EBM catalogue GOP 13620 (€ 16.58).

Treatment 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				
Patient population a1)				
Evolocumab	In cycles, 1 x every 14 or 1 x every 28 days	13.0 – 26.1	1	13.0 – 26.1
Simvastatin	continuously, 1 x daily	365	1	365
Cholestyramine	continuously, 1-3 x daily[11]	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
Patient population a2)				
Evolocumab	In cycles, 1 x every 14 or 1	13.0 – 26.1	1	13.0 – 26.1

[9] https://www.fachinfo.de/suche/fi/022075 (last access: 05.05.2022)
[10] http://www.aerztenetz-bad-berleburg.de/images/S2k-Leitlinie-Hyperlipidaemien-Kinder-Jugendliche.pdf (last access: 05.05.2022)
[11] 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 misinformation for adults.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	x every 28 days			
Simvastatin	continuously, 1 x daily	365	1	365
Cholestyramine	continuously, 1-3 x daily	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
LDL apheresis	In cycles, every 7 - every 14 days	26.1 – 52.1	1	26.1 – 52.1
Patient population b1)				
Evolocumab	In cycles, 1 x every 14 or 1 x every 28 days	13.0 – 26.1	1	13.0 – 26.1
Simvastatin	continuously, 1 x daily	365	1	365
Cholestyramine	continuously, 1-3 x daily	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
Patient population b2)				
Evolocumab	In cycles, 1 x every 14 or 1 x every 28 days	13.0 – 26.1	1	13.0 – 26.1
Simvastatin	continuously, 1 x daily	365	1	365
Cholestyramine	continuously, 1-3 x daily	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
LDL apheresis	In cycles, every 7 - every 14 days	26.1 – 52.1	1	26.1 – 52.1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Appropriate comparator therapy				
Patient population a1)				
Simvastatin	continuously, 1 x daily	365	1	365
Cholestyramine	continuously, 1-3 x daily	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
Patient population a2)				
Simvastatin	continuously, 1 x daily	365	1	365
Cholestyramine	continuously, 1-3 x daily	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
LDL apheresis	In cycles, every 7 - every 14 days	26.1 – 52.1	1	26.1 – 52.1
Patient population b1)				
Simvastatin	continuously, 1 x daily	365	1	365
Cholestyramine	continuously, 1-3 x daily	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
Patient population b2)				
Simvastatin	continuously, 1 x daily	365	1	365
Cholestyramine	continuously, 1-3 x daily	365	1	365
Ezetimibe	continuously, 1 x daily	365	1	365
LDL apheresis	In cycles, every 7 - every 14 days	26.1 – 52.1	1	26.1 – 52.1

Consumption:

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.

Designation of the therapy	Dosage	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Patient population a1)					
Evolocumab	140 mg - 420 mg	140 mg - 420 mg	1 x 140 mg - 1 x 420 mg	13.0 – 26.1	26.1 x 140 mg - 13.0 x 420 mg
Simvastatin	10 mg - 40 mg	10 mg - 40 mg	1 x 10 mg – 1 x 40 mg	365	365 x 10 mg – 365 x 40 mg
Cholestyramine	Child aged 10 years				
	2.2 g – 4.3 g	2.2 g – 12.9 g	3 x 0.7 g – 18 x 0.7 g[12]	365	1,095 x 0.7 g – 6,570 x 0.7 g
	Adolescents aged 17 years				
	3.8 g – 7.7 g	3.8 g – 23.0 g	1 x 4 g – 6 x 4 g	365	365 x 4 g – 2,190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Patient population a2)					
Evolocumab	140 mg - 420 mg	140 mg - 420 mg	1 x 140 mg - 1 x 420 mg	13.0 – 26.1	26.1 x 140 mg - 13.0 x 420 mg
Simvastatin	10 mg - 40 mg	10 mg - 40 mg	1 x 10 mg – 1 x 40 mg	365	365 x 10 mg – 365 x 40 mg
Cholestyramine	Child aged 10 years				
	2.2 g – 4.3 g	2.2 g – 12.9 g	3 x 0.7 g – 18 x 0.7 g	365	1,095 x 0.7 g – 6,570 x 0.7 g
	Adolescents aged 17 years				
	3.8 g – 7.7 g	3.8 g – 23.0 g	1 x 4 g – 6 x 4 g	365	365 x 4 g – 2,190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg

[12] 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/ patient/ year	Average annual consumption by potency
LDL apheresis	Not applicable			26.1 – 52.1	Not applicable
Patient population b1)					
Evolocumab	420 mg	420 mg	1 x 420 mg	13.0 – 26.1	13.0 x 420 mg - 26.1 x 420 mg
Simvastatin	10 mg - 40 mg	10 mg - 40 mg	1 x 10 mg – 1 x 40 mg	365	365 x 10 mg – 365 x 40 mg
Cholestyramine	Child aged 10 years				
	2.2 g – 4.3 g	2.2 g – 12.9 g	3 x 0.7 g - 18 x 0.7 g	365	1,095 x 0.7 g – 6,570 x 0.7 g
	Child aged 11 years				
	2.4 g – 4.8 g	2.4 g – 14.4 g	4 x 0.7 g – 4 x 4 g	365	1,460 x 0.7 g – 1,460 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Patient population b2)					
Evolocumab	420 mg	420 mg	1 x 420 mg	13.0 – 26.1	13.0 x 420 mg - 26.1 x 420 mg
Simvastatin	10 mg - 40 mg	10 mg - 40 mg	1 x 10 mg – 1 x 40 mg	365	365 x 10 mg – 365 x 40 mg
Cholestyramine	Child aged 10 years				
	2.2 g – 4.3 g	2.2 g – 12.9 g	3 x 0.7 g - 18 x 0.7 g	365	1,095 x 0.7 g – 6,570 x 0.7 g
	Child aged 11 years				
	2.4 g – 4.8 g	2.4 g – 14.4 g	4 x 0.7 g – 4 x 4 g	365	1,460 x 0.7 g – 1,460 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
LDL apheresis	Not applicable			26.1 – 52.1	Not applicable
Appropriate comparator therapy					
Patient population a1)					
Simvastatin	10 mg - 40 mg	10 mg - 40 mg	1 x 10 mg – 1 x 40 mg	365	365 x 10 mg – 365 x 40 mg
Cholestyramine	Child aged 10 years				

Designation of the therapy	Dosage	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ patient/ year	Average annual consumption by potency
	2.2 g - 4.3 g	2.2 g – 12.9 g	3 x 0.7 g – 18 x 0.7 g	365	1,095 x 0.7 g – 6,570 x 0.7 g
	Adolescents aged 17 years				
	3.8 g – 7.7 g	3.8 g – 23.0 g	1 x 4 g – 6 x 4 g	365	365 x 4 g – 2,190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Patient population a2)					
Simvastatin	10 mg - 40 mg	10 mg - 40 mg	1 x 10 mg – 1 x 40 mg	365	365 x 10 mg – 365 x 40 mg
Cholestyramine	Child aged 10 years				
	2.2 g – 4.3 g	2.2 g – 12.9 g	3 x 0.7 g – 18 x 0.7 g	365	1,095 x 0.7 g – 6,570 x 0.7 g
	Adolescents aged 17 years				
	3.8 g – 7.7 g	3.8 g – 23.0 g	1 x 4 g – 6 x 4 g	365	365 x 4 g – 2,190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
LDL apheresis	Not applicable			26.1 – 52.1	Not applicable
Patient population b1)					
Simvastatin	10 mg - 40 mg	10 mg - 40 mg	1 x 10 mg – 1 x 40 mg	365	365 x 10 mg – 365 x 40 mg
Cholestyramine	Child aged 10 years				
	2.2 g – 4.3 g	2.2 g – 12.9 g	3 x 0.7 g – 18 x 0.7 g	365	1,095 x 0.7 g – 6,570 x 0.7 g
	Child aged 11 years				
	2.4 g – 4.8 g	2.4 g – 14.4 g	4 x 0.7 g – 4 x 4 g	365	1,460 x 0.7 g – 1,460 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Patient population b2)					
Simvastatin	10 mg - 40 mg	10 mg - 40 mg	1 x 10 mg – 1 x 40 mg	365	365 x 10 mg – 365 x 40 mg
Cholestyramine	Child aged 10 years				
	2.2 g – 4.3 g	2.2 g – 12.9 g	3 x 0.7 g – 18 x 0.7 g	365	1,095 x 0.7 g – 6,570 x 0.7 g

Designation of the therapy	Dosage	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ patient/ year	Average annual consumption by potency
	Child aged 11 years				
	2.4 g – 4.8 g	2.4 g – 14.4 g	4 x 0.7 g – 4 x 4 g	365	1,460 x 0.7 g – 1,460 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
LDL apheresis	Not applicable			26.1 – 52.1	Not applicable

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.

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					
Evolocumab 140 mg	6 PEN	€ 1,433.87	€ 1.77	€ 78.76	€ 1,353.34
Evolocumab 420 mg	3 SFI	€ 1,551.68	€ 1.77	€ 85.33	€ 1,464.58
Cholestyramine 0.74 g[13]	400 g GOS	€ 53.35	€ 1.77	€ 3.33	€ 48.25
Cholestyramine 4 g[13]	100 POS	€ 66.71	€ 1.77	€ 4.38	€ 60.56
Ezetimibe 10 mg[13]	100 TAB	€ 34.05	€ 1.77	€ 1.80	€ 30.48
Simvastatin 10 mg[13]	100FTA	€ 13.96	€ 1.77	€ 0.21	€ 11.98
Simvastatin 40 mg[13]	100 FCT	€ 21.67	€ 1.77	€ 0.82	€ 19.08

[13] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
LDL apheresis	Not applicable				€ 885.78 – € 1,294.81
Appropriate comparator therapy					
Cholestyramine 0.74 g[13]	400 g GOS	€ 53.35	€ 1.77	€ 3.33	€ 48.25
Cholestyramine 4 g[13]	100 POS	€ 66.71	€ 1.77	€ 4.38	€ 60.56
Ezetimibe 10 mg[13]	100 TAB	€ 34.05	€ 1.77	€ 1.80	€ 30.48
Simvastatin 10 mg[13]	100FTA	€ 13.96	€ 1.77	€ 0.21	€ 11.98
Simvastatin 40 mg[13]	100 FCT	€ 21.67	€ 1.77	€ 0.82	€ 19.08
LDL apheresis	Not applicable				€ 885.78 – € 1,294.81
Abbreviations: FTA = film-coated tablets, GOS = granules for the preparation of an oral suspension, SFI = solution for injection, PEN = solution for injection in a pre-filled pen, POS = powder for the preparation of an oral suspension, TAB = tablets					

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Costs for additionally required SHI services:

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

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

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

3. Bureaucratic costs 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 10 March 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 21 December 2021, the pharmaceutical company submitted a dossier for the benefit assessment of evolocumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 22 December 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient evolocumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 March 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 April 2022. The deadline for submitting written statements was 22 April 2022.

The oral hearing was held on 9 May 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

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

At its session on 16 June 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 March 2021	Determination of the appropriate comparator therapy
Working group Section 35a	3 May 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 May 2022	Conduct of the oral hearing
Working group Section 35a	17 May 2022 31 May 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	8 June 2022	Concluding discussion of the draft resolution

Plenum	16 June 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 June 2022

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

Prof. Hecken