Gemeinsamer Bundesausschuss

Justification

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

of 15 July 2021

Contents

1. Legal basis

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

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient inclisiran in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 February 2021. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 29 January 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de), on 3 May 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of inclisiran 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 inclisiran.

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 inclisiran (Leqvio) in accordance with the product information

Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, 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.

Therapeutic indication of the resolution (resolution of 15 July 2021):

see therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for inclisiran:

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

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

Appropriate comparator therapy for inclisiran:

[1] General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

– Evolocumab[2] or alirocumab or LDL apheresis (as an "ultima ratio" for therapy-refractory courses), if necessary with concomitant medicinal-based 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 Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. For the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia is approved in the therapeutic indication: HMG-CoA reductase inhibitors (statins), fibrates, anion exchange resins (bile acid binders), ezetimibe as a cholesterol resorption inhibitor, and the PCSK9 inhibitors evolocumab and alirocumab.

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

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

- The G-BA has made the following resolutions on the benefit assessment for the therapeutic indication to be considered in this procedure:
  – bempedoic acid (Resolution of 15 April 2021),
  – bempedoic acid/ezetimibe (resolution of 14 April 2021),

[2] The requirements regarding the prescription restriction of the Pharmaceutical Directive (AM-RL) Annex III must be observed.

- evolocumab (resolution of 9 March 2016; resolution of 6 September 2018 - new benefit assessment pursuant to Section 14 VerfO),
- alirocumab (resolution of 4 May 2016, resolution of 2 May 2019 - benefit assessment pursuant to Section 14 VerfO),
- lomitapide (Resolution of 27 November 2015).

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

- Therapy information (AM-RL Annex IV): the therapy information for the active ingredient ezetimibe (G-BA resolution of 17 December 2009) was repealed by a resolution of 22 November 2018. An IQWiG report on the benefit assessment of ezetimibe (Rapid Report Version 2.0) from 3.9.2019 is available.

- The guideline of the Federal Joint Committee on examination and treatment methods for statutory medical care regulates in Annex I: Recognised examination or treatment methods - the requirements for the implementation and billing of apheresis within the framework of statutory medical care. According to this guideline, highly effective standard medication therapies are generally available in contract medical care, so that apheresis should only be used in exceptional cases as the "ultima ratio" in the case of therapy-refractory courses. For example, LDL apheresis can only be carried out in homozygous patients with familial hypercholesterolaemia or in patients with severe

hypercholesterolaemia in whom the LDL cholesterol cannot be sufficiently reduced with a maximum dietary and medicinal therapy documented for over twelve months. The overall risk profile of the patient should be in the foreground when considering the indication.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

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

In all guidelines relevant in the therapeutic indication, medicinal product therapy with statins is named as the standard in the care of patients with hypercholesterolaemia. The influence of statins on cardiovascular events has been investigated in several randomised, controlled 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 LDLC values sufficiently, adjunctive therapy with ezetimibe is recommended. For ezetimibe, the IMPROVE-IT study[3] presented a cardiovascular endpoint study that showed statistically significant differences in the primary morbidity endpoint compared to therapy with simvastatin alone. For the other lipid-lowering agents (fibrates or anion exchangers), the available evidence with regard to the influence on patient-relevant endpoints is limited. Against this background, fibrates, in particular, are not determined as part of the appropriate comparator therapy.

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

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

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

The PCSK-9 inhibitors evolocumab and alirocumab are alternatives to LDL apheresis. Evolocumab and alirocumab can thus - in compliance with the Ordinance restrictions in Annex III - as another option for patients for whom the other lipid-lowering therapy

[3] Cannon CP, Blazing MA, Giuliano RP, et al: Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372: 23872397

options have been exhausted are applied. Evolocumab, alirocumab and LDL apheresis are equally appropriate treatment options for patient group b).

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

In patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, in whom medicinal and dietary options for lipid-lowering 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 corresponds to the individually maximally tolerated medicinal therapy has not yet been exhausted, not the implementation of the appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

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

An additional benefit is not proven.

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

An additional benefit is not proven.

Justification:

Patient group a)

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

Patient group b)

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

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Leqvio with active ingredient inclisiran.

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

- in combination with a statin or 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.

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

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

As appropriate comparator therapy was a maximum tolerated medicinal therapy according to the doctor's instructions statins, Cholesterin resorption inhibitors and determines anion exchangers.

No data were presented versus the appropriate comparator therapy. An additional benefit is not proven.

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

Evolocumab or alirocumab or LDL apheresis (as the "ultima ratio" in the case of therapy-refractory courses), possibly with concomitant medicinal- reducing lipid-lowering agents therapy, was determined as the appropriate comparator therapy

No data were presented versus the appropriate comparator therapy. An additional benefit is not proven.

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

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

The information provided by the pharmaceutical company in the dossier is generally fraught with uncertainties.

Firstly, not all statins available on the market were considered. Second, the assessment for LDL target achievement is based solely on a recorded LDL-C value. From a clinical point of view, however, the LDL-C level may be subject to fluctuations, so that several LDL-C values over time would have been necessary for this purpose. The exclusive inclusion of patients with only one documented LDL-C level potentially results in an overestimation of the target population. In addition, almost half of the patients did not have a documented LDL-C value, which further contributes to the uncertainties mentioned above.

Patient group a)

Despite the limitations described above, the total number of patients in the SHI target population is based on the upper limit of 410,915 adults, according to the information in the pharmaceutical company's dossier.

Against the background of the limitations of the pharmaceutical company's approach and due to the fact that the patient figures submitted deviate from the patient figures already published, the G-BA considers it appropriate to create a range in which the patient figures already published are taken into account. Therefore, as a lower limit, the data as in the previous resolutions in the therapeutic indication of hypercholesterolaemia or mixed dyslipidaemia in the corresponding patient groups[4, 5, 6] are taken into account. For the upper limit of the patient group a) to be considered here, the figure corresponding to the total SHI target population minus approx. 21,000 adults is used as a basis in accordance with the upper limit of patient group b).

Patient group b)

In patient group b), too, it is considered appropriate to define a range due to the uncertainties already mentioned.

In the lower limit, the already published patient numbers are taken into account accordingly[6].

The upper limit takes into account the information from the pharmaceutical company's dossier regarding the number of patients for whom a prescription for alirocumab or evolocumab was identified, plus those adults with apheresis treatment due to severe hypercholesterolaemia.

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

[4] https://www.g-ba.de/downloads/91-1385-407/2019-05-02_Geltende-Fassung_Alirocumab_D-194_D-409.pdf
[5] https://www.g-ba.de/downloads/91-1385-354/2018-09-06_Geltende-Fassung_Evolocumab_D-345.pdf
[6] https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/604/#beschluesse

product characteristics, SmPC) for Leqvio (active ingredient: inclisiran) at the following publicly accessible link (last access: 8 June 2021):

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

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 June 2021).

Costs of the medicinal product:

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

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

Medicinal product to be assessed: Inclisiran

The recommended dosage of Inclisiran is 284 mg every 6 months, according to the product information.

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

Since a maximum tolerable statin dose is assumed in the present therapeutic indication, simvastatin therapy in a dosage range of approximately 40 mg to 80 mg daily (in patients with a high risk of cardiovascular complications) is used as an example for the cost calculation.

For the combination of inclisiran with other lipid-lowering agents besides a statin or in addition to a statin, combinations with ezetimibe and colesevelam or cholestyramine were presented as examples for the calculation of the annual treatment costs.

Appropriate comparator therapy

Medicinal lipid-lowering agents therapy

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

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

- Anion exchanger: For calculating the treatment costs, both the costs for colesevelam and cholestyramine were shown. The daily dose of cholestyramine for adults is 1 - 4 sachets per day or a maximum of 6 sachets per day. The recommended daily dose of colesevelam in monotherapy is from 3.75 to 4,375 g (6 - 7 tablets), in combination with ezetimibe, with or without a statin, the recommended 2.5 - 3.75 g (4 - 6 tablets). The presentation of the annual treatment costs occurs according to the appropriate comparator therapy, exclusively taking into account the maximum dosage.
- Cholesterol absorption inhibitors: ezetimibe The recommended dosage is 10 mg per day.

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

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

For the calculation of the annual treatment costs under monotherapy with alirocumab, the recommended dosages in the product information of either 75 mg alirocumab every two weeks or, in patients requiring a greater LDL-C reduction (> 60%), the administration of 150 mg (every two weeks) or 300 mg alirocumab (every four weeks), both as subcutaneous administration, are used.

Non-medicinal lipid-lowering agents therapy: LDL apheresis

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

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Patient population a)				
Inclisiran	continuously, once every 182.5 days[7]	2	1	2
Simvastatin	continuously, once daily	365	1	365
Colesevelam	continuously, once or twice daily	365	1	365
Cholestyramine	continuously, 1-3 times a day	365	1	365
Ezetimibe	continuously, once daily	365	1	365
Patient population b)				
Inclisiran	In cycles, once every 182.5 days	2	1	2
Simvastatin	continuously, once daily	365	1	365
Colesevelam	continuously, once or twice daily	365	1	365
Cholestyramine	continuously, 1-3 times a day	365	1	365

[7] 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

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Cholestyramine	continuously, 1-3 times a day	365	1	365
Ezetimibe	continuously, once daily	365	1	365
LDL apheresis	In cycles, every 7 - every 14 days	26.1 – 52.1	1	26.1 – 52.1

Consumption:

Designation of the therapy	Dosage	Dosage/patient/days of treatment	Usage by potency/day of treatment	Days of treatment / patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Patient population a)					
Inclisiran	284 mg	284 mg	1 x 284 mg	2	2 x 284 mg
Simvastatin	40 mg - 80 mg	40 mg - 80 mg	1 x 40 mg - 1 x 80 mg	365	365 x 40 mg - 365 x 80 mg
Colesevelam[8]	2.5 g - 3.75 g	2.5 g - 3.75 g	4 x 625 mg - 6 x 625 mg	365	1,460 x 625 mg - 2,190 x 625 mg
Cholestyramine	4 g - 8 g	4 g - 24 g	1 x 4 g - 6 x 4 g	365	365 x 4 g - 2 190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Patient population b)					

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

Designation of the therapy	Dosage	Dosage/patient/days of treatment	Usage by potency/day of treatment	Days of treatment / patient/ year	Average annual consumption by potency
Inclisiran	284 mg	284 mg	1 x 284 mg	2	2 x 284 mg
Simvastatin	40 mg - 80 mg	40 mg - 80 mg	1 x 40 mg - 1 x 80 mg	365	365 x 40 mg - 365 x 80 mg
Colesevelam[8]	2.5 g - 3.75 g	2.5 g - 3.75 g	4 x 625 mg 6 x 625 mg	365	1,460 x 625 mg 2,190 x 625 mg
Cholestyramine	4 g - 8 g	4 g - 24 g	1 x 4 g 6 x 4 g	365	365 x 4 g - 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
Appropriate comparator therapy					
Patient population a)					
Simvastatin	40 mg - 80 mg	40 mg - 80 mg	1 x 40 mg - 1 x 80 mg	365	365 x 40 mg - 365 x 80 mg
Colesevelam[8]	2.5 g - 3.75 g	2.5 g - 3.75 g	4 x 625 mg - 6 x 625 mg	365	1,460 x 625 mg - 2,190 x 625 mg
Cholestyramine	4 g - 8 g	4 g - 24 g	1 x 4 g - 6 x 4 g	365	365 x 4 g - 2,190 x 4 g
Ezetimibe	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Patient population b)					
Evolocumab	140 mg –	140 mg – 420 mg	1 x 140 mg - 1 x 420 mg	13.0 – 26.1	26.1 x 140 mg -

Designation of the therapy	Dosage	Dosage/patient/days of treatment	Usage by potency/day of treatment	Days of treatment / patient/ year	Average annual consumption by potency
	420 mg				13.0 x 420 mg
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				
	300 mg	300 mg	1 x 300 mg	13.0	13.0 x 300 mg
Simvastatin	40 mg - 80 mg	40 mg - 80 mg	1 x 40 mg - 1 x 80 mg	365	365 x 40 mg - 365 x 80 mg
Colesevelam[8]	2.5 g - 3.75 g	2.5 g - 3.75 g	4 x 625 mg - 6 x 625 mg	365	1,460 x 625 mg - 2,190 x 625 mg
Cholestyramine	4 g - 8 g	4 g - 24 g	1 x 4 g - 6 x 4 g	365	3 65 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

Costs:

Costs of the medicinal product:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate § 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Inclisiran	1 SFI	€ 2,896.10	€ 1.77	€ 162.12	€ 2,732.21

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate § 130a SGB V	Costs after deduction of statutory rebates
Colesevelam 625 mg	180 FCT	€ 205.37	€ 1.77	€ 10.76	€ 192.84
Cholestyramine[9] 4 g	400 GSE	€ 53.11	€ 1.77	€ 3.33	€ 48.01
Ezetimibe[9] 10 mg	100 TAB	€ 45.43	€ 1.77	€ 2.72	€ 40.94
Simvastatin[9] 40 mg	100 FCT	€ 21.43	€ 1.77	€ 0.82	€ 18.84
Simvastatin[9] 80 mg	100 FCT	€ 30.18	€ 1.77	€ 1.51	€ 26.90
LDL apheresis	Not applicable				€ 885.78 – € 1,294.81
Appropriate comparator therapy					
Colesevelam 625 mg	180 FCT	€ 205.37	€ 1.77	€ 10.76	€ 192.84
Cholestyramine[9] 4 g	400 GSE	€ 53.11	€ 1.77	€ 3.33	€ 48.01
Evolocumab 140 mg	6 PEN	€ 1, 433.63	€ 1.77	€ 78.76	€ 1,353.10
Evolocumab 420 mg	3 SFI	€ 1,551.44	€ 1.77	€ 85.33	€ 1,464.34
Alirocumab 75 mg	6 SFI	€ 1, 433.63	€ 1.77	€ 0.00	€ 1,431.86
Alirocumab 300 mg	3 SFI	€ 1,551.44	€ 1.77	€ 0.00	€ 1,549.67
Ezetimibe[9] 10 mg	100 TAB	€ 45.43	€ 1.77	€ 2.72	€ 40.94
Simvastatin[9] 40 mg	100 FCT	€ 21.43	€ 1.77	€ 0.82	€ 18.84
Simvastatin[9] 80 mg	100 FCT	€ 30.18	€ 1.77	€ 1.51	€ 26.90
LDL apheresis	Not applicable				€ 885.78 – € 1,294.81
Abbreviations: FCT= film-coated tablets, GSE = granules for the preparation of a suspension for oral use, SFI = solution for injection, PEN = ready-to-use pen, 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

[9]Fixed reimbursement rate

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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy according to 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 27 October 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 January 2021, the pharmaceutical company submitted a dossier for the benefit assessment of Inclisiran to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 1 February 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 Inclisiran.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 April 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 3 May 2021. The deadline for submitting written statements was 25 May 2021.

The oral hearing was held on 8 June 2021.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 July 2021, and the proposed resolution was approved.

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	27 October 2020	Determination of the appropriate comparator therapy
Working group Section 35a	2 June 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal product	8 June 2021	Conduct of the oral hearing
Working group Section 35a	16 June 2021 30 June 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	6 July 2021	Concluding discussion of the draft resolution
Plenum	15 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 July 2021

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

Prof. Hecken