Gemeinsamer Bundesausschuss

# Resolution

of the Federal Joint Committee 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

At its session on 16 June 2022, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

**I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Evolocumab in accordance with the resolution of 6 September 2018:**

**Evolocumab**

Resolution of: 16 June 2022
Entry into force on: 16 June 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

**New therapeutic indication (according to the marketing authorisation of 26 November 2021):**

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:

- 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.

## 1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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

**Extent and probability of the additional benefit of evolocumab compared to the appropriate comparator therapy:**

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

**Appropriate comparator therapy:**

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

**Extent and probability of the additional benefit of evolocumab compared to the appropriate comparator therapy:**

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

**Appropriate comparator therapy:**

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

**Extent and probability of the additional benefit of evolocumab compared to the appropriate comparator therapy:**

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

**Appropriate comparator therapy:**

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

**Extent and probability of the additional benefit of Evolocumab compared to the appropriate comparator therapy:**

An additional benefit is not proven.

**Study results according to endpoints:**[1]

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

There are no assessable data for the benefit assessment.

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| Mortality | n.a. | There are no assessable data. |
| Morbidity | n.a. | There are no assessable data. |
| Health-related quality of life | ∅ | No data available. |
| Side effects | n.a. | There are no assessable data. |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |

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 available.

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| Mortality | ∅ | No data available. |
| Morbidity | ∅ | No data available. |
| Health-related quality of life | ∅ | No data available. |
| Side effects | ∅ | No data available. |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data | | |

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-171) unless otherwise indicated.

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| ↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |

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

There are no assessable data for the benefit assessment.

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| Mortality | n.a. | There are no assessable data. |
| Morbidity | n.a. | There are no assessable data. |
| Health-related quality of life | ∅ | No data available. |
| Side effects | n.a. | There are no assessable data. |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |

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 available.

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| Mortality | ∅ | No data available. |
| Morbidity | ∅ | No data available. |
| Health-related quality of life | ∅ | No data available. |
| Side effects | ∅ | No data available. |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference | | |

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| ∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |

## 2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 760 - 940 patients

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

approx. 6 patients

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

approx. 1 - 2 patients

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

approx. 1 - 2 patients

## 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.

## 4. Treatment costs

**Annual treatment costs:**

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

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Medicinal product to be assessed: | |
| Evolocumab as monotherapy | € 5,887.03 - € 6,346.51 |
| Simvastatin[2] | € 43.73 - € 69.64 |
| Cholestyramine | € 132.08 - € 1,326.26 |
| Ezetimibe | € 111.25 |
| *Evolocumab in combination with other lipid-lowering therapies (including statin)* | |
| Evolocumab + simvastatin[2] | € 5,930.76 - € 6,416.15 |
| Evolocumab + simvastatin[2] + ezetimibe | € 6,042.01 - € 6,527.40 |
| Evolocumab + simvastatin[2] + cholestyramine | € 6,062.84 - € 7,742.41 |
| Evolocumab + simvastatin [2]+ cholestyramine + ezetimibe | € 6,174.09 - € 7,853.66 |
| *Evolocumab in combination with other lipid-lowering therapies (except statin)* | |
| Evolocumab + ezetimibe | € 5,998.28 - € 6,457.76 |
| Evolocumab + cholestyramine | € 6,019.11 - € 7,672.77 |
| Evolocumab + cholestyramine + ezetimibe | € 6,130.36 - € 7,784.02 |
| Appropriate comparator therapy: | |
| Monotherapy | |
| Simvastatin[2] | € 43.73 - € 69.64 |
| Cholestyramine | € 132.08 - € 1,326.26 |
| Ezetimibe | € 111.25 |
| Combination therapies | |
| Simvastatin[2] + ezetimibe | € 154.98 - € 180.89 |
| Simvastatin[2] + cholestyramine | € 175.81 - € 1395.90 |
| Simvastatin[2] + cholestyramine + ezetimibe | € 287.06 - € 1,507.15 |
| Ezetimibe + cholestyramine | € 243.33 - € 1,437.51 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2022

Costs for additionally required SHI services: not applicable

[2] Simvastatin is shown as example for the statin 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

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Medicinal product to be assessed: | |
| Evolocumab as monotherapy | € 5,887.03 - € 6,346.51 |
| Simvastatin[2] | € 43.73 - € 69.64 |
| Ezetimibe | € 111.25 |
| Cholestyramine | € 132.08 - € 1,326.26 |
| LDL apheresis | € 23,118.86 - € 67,459.60 |
| Evolocumab + LDL apheresis | € 29,005.89 - € 73,806.11 |
| *Evolocumab in combination with other lipid-lowering therapies (including statin) including LDL apheresis* | |
| Evolocumab + simvastatin[2] + LDL apheresis | € 29,049.62 - € 73,875.75 |
| Evolocumab + simvastatin[2] + ezetimibe + LDL apheresis | € 29,160.87 - € 73,987.00 |
| Evolocumab + simvastatin[2] + ezetimibe + cholestyramine + LDL apheresis | € 29,292.95 - € 75,313.26 |
| *Evolocumab in combination with other lipid-lowering therapies (excluding statin) including LDL apheresis* | |
| Evolocumab + ezetimibe + LDL apheresis | € 29,117.14 - € 73,917.36 |
| Evolocumab + cholestyramine + LDL apheresis | € 29,137.97 - € 75,132.37 |
| Evolocumab + ezetimibe + cholestyramine + LDL-apheresis | € 29,249.22 - € 75,243.62 |
| Appropriate comparator therapy: | |
| LDL apheresis | € 23,118.86 - € 67,459.60 |
| *LDL apheresis if necessary + accompanying medicinal lipid-lowering therapy (including statin)* | |
| LDL apheresis if necessary + simvastatin[2] | € 23,162.59 - € 67,529.24 |
| LDL apheresis if necessary + simvastatin[2] + ezetimibe | € 23,273.84 - € 67,640.49 |
| LDL apheresis if necessary + simvastatin[2] + cholestyramine | € 23,294.67 - € 68,855.50 |
| LDL apheresis if necessary + simvastatin[2] + ezetimibe + cholestyramine | € 23,405.92 - € 68,966.75 |
| *LDL apheresis if necessary + accompanying medicinal lipid-lowering therapy (except statin)* | |
| LDL apheresis if necessary + ezetimibe | € 23,230.11 - € 67,570.85 |
| LDL apheresis if necessary + cholestyramine | € 23,250.94 - € 68,785.86 |
| LDL apheresis if necessary + ezetimibe + cholestyramine | € 23,362.19 - € 68,897.11 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2022

Costs for additionally required SHI services: not applicable

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

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Medicinal product to be assessed: | |
| Evolocumab as monotherapy | € 6,346.51 - € 12,741.85 |
| Simvastatin[2] | € 43.73 - € 69.64 |
| Cholestyramine | € 132.08 - € 884.18 |
| Ezetimibe | € 111.25 |
| *Evolocumab in combination with other lipid-lowering therapies (including statin)* | |
| Evolocumab + simvastatin[2] | € 6,390.24 - € 12,811.49 |
| Evolocumab + simvastatin[2] + ezetimibe | € 6,501.49 - € 12,922.74 |
| Evolocumab + simvastatin[2] + cholestyramine | € 6,522.32 - € 13,695.67 |
| Evolocumab + simvastatin[2] + cholestyramine + ezetimibe | € 6,633.57 - € 13,806.92 |
| *Evolocumab in combination with other lipid-lowering therapies (except statin)* | |
| Evolocumab + ezetimibe | € 6,457.76 - € 12,853.10 |
| Evolocumab + cholestyramine | € 6,478.59 - € 13,626.03 |
| Evolocumab + cholestyramine + ezetimibe | € 6,589.84 - € 13,737.28 |
| Appropriate comparator therapy: | |
| Monotherapy | |
| Simvastatin[2] | € 43.73 - € 69.64 |
| Cholestyramine | € 132.08 - € 884.18 |
| Ezetimibe | € 111.25 |
| Combination therapies | |
| Simvastatin[2] + ezetimibe | € 154.98 - € 180.89 |
| Simvastatin[2] + cholestyramine | € 175.81 - € 953.82 |
| Simvastatin[2] + cholestyramine + ezetimibe | € 287.06 - € 1065.07 |
| Ezetimibe + cholestyramine | € 243.33 - € 995.43 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2022

Costs for additionally required SHI services: not applicable

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

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Medicinal product to be assessed: | |
| Evolocumab as monotherapy | € 6,346.51 - € 12,741.85 |
| Simvastatin[2] | € 43.73 - € 69.64 |
| Ezetimibe | € 111.25 |
| Cholestyramine | € 132.08 - € 884.18 |
| LDL apheresis | € 23,118.86 - € 67,459.60 |
| Evolocumab + LDL apheresis | € 29,465.37 - € 80,201.45 |
| *Evolocumab in combination with other lipid-lowering therapies (including statin) including LDL apheresis* | |
| Evolocumab + simvastatin[2] + LDL apheresis | € 29,509.10 - € 80,271.09 |
| Evolocumab + simvastatin[2] + ezetimibe + LDL apheresis | € 29,620.35 - € 80,382.34 |
| Evolocumab + simvastatin[2] + ezetimibe + cholestyramine + LDL apheresis | € 29,752.43 - € 81,266.52 |
| *Evolocumab in combination with other lipid-lowering therapies (excluding statin) including LDL apheresis* | |
| Evolocumab + ezetimibe + LDL apheresis | € 29,576.62 - € 80,312.70 |
| Evolocumab + cholestyramine + LDL apheresis | € 29,597.45 - € 81,085.63 |
| Evolocumab + ezetimibe + cholestyramine + LDL-apheresis | € 29,708.70 - € 81,196.88 |
| Appropriate comparator therapy: | |
| LDL apheresis | € 23,118.86 - € 67,459.60 |
| LDL apheresis if necessary + accompanying medicinal lipid-lowering therapy (including statin) | |
| LDL apheresis if necessary + simvastatin[2] | € 23,162.59 - € 67,529.24 |
| LDL apheresis if necessary + simvastatin[2] + ezetimibe | € 23,273.84 - € 67,640.49 |
| LDL apheresis if necessary + simvastatin + cholestyramine | € 23,294.67 - € 68,413.42 |
| LDL apheresis if necessary + simvastatin[2] + ezetimibe + cholestyramine | € 23,405.92 - € 68,524.67 |
| *LDL apheresis if necessary + accompanying medicinal lipid-lowering therapy (except statin)* | |
| LDL apheresis if necessary + ezetimibe | € 23,230.11 - € 67,570.85 |
| LDL apheresis if necessary + cholestyramine | € 23,250.94 - € 68,343.78 |
| LDL apheresis if necessary + ezetimibe + cholestyramine | € 23,362.19 - € 68,455.03 |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2022

Costs for additionally required SHI services: not applicable

**II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 June 2022.**

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 16 June 2022

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

Prof. Hecken