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 Nirsevimab (new therapeutic indication: secondary prevention of RSV infections, children during their 2nd RSV season, ≤ 24 months of life)

of 20 February 2025

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

On 1 August 2024, nirsevimab 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, sentence 7).

On 15 August 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient nirsevimab with the new therapeutic indication "Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower

respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season." in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The assessment only includes children in their second RSV season with an indication for secondary prevention according to the therapeutic indication for respiratory syncytial virus antibodies (Annex IV to the Pharmaceuticals Directive (AM-RL)).

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

Based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, the G-BA decided on the question on whether an additional benefit of nirsevimab compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by IQWiG according to the General Methods was not used in the benefit assessment of risankizumab – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Nirsevimab (Beyfortus) in accordance with the product information

Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

Beyfortus should be used in accordance with official recommendations.

Therapeutic indication of the resolution (resolution of 20 February 2025):

Prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in children up to 24 months of age with indication for secondary prevention during their second RSV season.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is indicated

Appropriate comparator therapy for nirsevimab:

– Palivizumab

b) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is not indicated

Appropriate comparator therapy for nirsevimab:

– Monitoring wait-and-see approach

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application, unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

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

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

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

on 1. In addition to nirsevimab, the active ingredient palivizumab is approved in the therapeutic indication for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in children up to 24 months of age with indication for secondary prevention.

on 2. Non-medicinal treatment alone is not an option for the prevention of RSV-related lower respiratory tract infections.

on 3. For the prevention of RSV-related lower respiratory tract infections, there is a resolution from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

- Nirsevimab (secondary prevention of RSV infections, children during their 1st RSV season) from 15 August 2024

Furthermore, the therapeutic information on respiratory syncytial virus antibodies (Pharmaceuticals Directive Annex IV - Therapeutic information in accordance with Section 92, paragraph 2, sentence 7 SGB V) dated 2 November 2023 must be taken into account.

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.

The present body of evidence includes a systematic review and a Cochrane review besides the German S2k guideline "On the prevention of severe respiratory syncytial virus (RSV) disease in at-risk children".

According to the therapeutic information on RSV antibodies (Pharmaceuticals Directive Annex IV - Therapeutic information pursuant to Section 92, paragraph 2, sentence 7 SGB V) dated 2 November 2023, the intervention is a secondary prevention for the following children:

Children at a high risk of severe courses of infection aged ≤ 24 months at the start of the RSV season who required concomitant therapeutic measures due to bronchopulmonary dysplasia within the last six months prior to the RSV season, children with haemodynamically relevant heart defects and children with trisomy 21.

In the overall assessment, a recommendation for targeted prevention with palivizumab can also be derived from the aggregated evidence for a) Children during their 2nd RSV season up to 24 months of age with an indication for secondary prevention of lower respiratory tract infections caused by RSV in whom palivizumab is indicated. The therapeutic information on RSV antibodies (Pharmaceuticals Directive Annex IV - Therapeutic information pursuant to Section 92, paragraph 2, sentence 7 SGB V) dated

2 November 2023 is taken into account accordingly - particularly with regard to palivizumab suitability - in the indication.

The patient population b) Children during their 2nd RSV season up to 24 months of age with an indication for secondary prevention of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated, comprises children with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically relevant heart defects), taking into account the therapeutic information on RSV antibodies (Pharmaceuticals Directive Annex IV - Therapeutic information in accordance with Section 92, paragraph 2, sentence 7 SGB V) of 2 November 2023. In the absence of other available therapy options, the monitoring wait-and-see approach is determined as the appropriate comparator therapy for nirsevimab as the active ingredient palivizumab is not approved for RSV prevention in children with trisomy 21.

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

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

2.1.3 Extent and probability of the additional benefit

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

a) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is indicated

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company submits results of the MEDLEY study. The study is a completed double-blind RCT comparing nirsevimab versus palivizumab in children in their 1st and 2nd RSV season. The pharmaceutical company presented the results of the final analysis of the 2nd RSV season.

For the present assessment, only the period of the 2nd RSV season is considered. For the efficacy endpoints, the pharmaceutical company used evaluations from day 151 of the 2nd RSV season, and for the safety endpoints, evaluations from day 361 of the 2nd RSV season.

The MEDLEY study comprises two cohorts, one cohort of preterm infants and another cohort of children with a history of bronchopulmonary dysplasia and/or a haemodynamically relevant congenital heart defect.

The study population in the 2nd RSV season solely comprises children from the cohort of children with a history of bronchopulmonary dysplasia and/or a haemodynamically relevant congenital heart defect. This cohort enrolled children who had bronchopulmonary dysplasia, due to which they required medical interventions such as supplemental oxygen, bronchodilators or diuretics within 6 months prior to randomisation, as well as children with a haemodynamically relevant congenital heart defect that had not yet been corrected or had only been partially corrected.

All 262 children of the originally 310 randomised children from the cohort who completed the follow-up in the 1st RSV season remained in the study and moved onto the 2nd RSV season. These children were also treated in the 2nd RSV season with nirsevimab or palivizumab as part of the study. Children who received nirsevimab in the 1st RSV season, were reassigned to the nirsevimab arm for the 2nd RSV season. Children who received palivizumab in the 1st RSV season were randomised again in a 1:1 ratio to treatment with nirsevimab or palivizumab for the 2nd RSV season. Nirsevimab and palivizumab were each dosed according to the product information.

The primary endpoint of the study was the assessment of safety and tolerability based on endpoints in the side effects category. Patient-relevant secondary endpoints were collected in the morbidity category.

Of the children who were treated with nirsevimab or palivizumab in their 2nd RSV season, 189 children had bronchopulmonary dysplasia that required treatment within the last 6 months and 81 children had a haemodynamically relevant congenital heart defect at the time of randomisation before the 1st RSV season. 9 children had both bronchopulmonary dysplasia and a haemodynamically relevant congenital heart defect.

In the MEDLEY study, it was nevertheless not rechecked at the beginning of the 2nd RSV season whether the children with bronchopulmonary dysplasia had required relevant medical measures in the previous 6 months. It therefore remains unclear whether the included children with bronchopulmonary dysplasia, who required treatment for this within the previous 6 months prior to the 1st RSV season, continued to have an indication for secondary prevention with an RSV antibody in their 2nd RSV season.

Likewise, for the sub-population of children with haemodynamically relevant congenital heart defects, there is no updated information on disease history or details of existing medication or surgical interventions on day 1 of the 2nd RSV season. For these children, it can therefore not be ruled out that at least in some of them the haemodynamically relevant changes have completely regressed or have been corrected by surgical interventions between their 1st and 2nd RSV season. In these cases, there would no longer be an increased risk of a severe course of RSV infection of the lower respiratory tract and there would no longer be an indication for secondary prevention with an RSV antibody for these children during their 2nd RSV season.

Overall, it therefore remains unclear to what extent the children with a history of bronchopulmonary dysplasia and/or a haemodynamically relevant congenital heart defect continued to have an increased risk of a severe course of RSV infection of the lower respiratory tract and thus the indication for secondary prevention with nirsevimab or palivizumab in their 2nd RSV season.

Therefore, no suitable data are available to assess the additional benefit of nirsevimab compared with the appropriate comparator therapy in children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is indicated. An additional benefit is therefore not proven.

b) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is not indicated

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company cites the single-arm MUSIC study. Immunocompromised children in their 1st or 2nd year of life, who entered their 1st or 2nd RSV season at the time of the 1st nirsevimab administration, were enrolled in the MUSIC study.

The patient population b) includes children with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically relevant heart defects). The active ingredient palivizumab is not approved for these children. However, children with trisomy 21 were generally excluded from participation in the MUSIC study. Consequently, no suitable data are available for the patient population to be assessed.

In addition, the single-arm MUSIC study does not allow a comparison with the determined appropriate comparator therapy.

Therefore, no suitable data are available to assess the additional benefit of nirsevimab compared with the appropriate comparator therapy in children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is not indicated. An additional benefit is therefore 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 nirsevimab.

The therapeutic indication assessed here is as follows: "Prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season."

A distinction was made between two patient populations in the therapeutic indication to be considered.

a) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is indicated

The G-BA determined a therapy with palivizumab as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company submits results of the MEDLEY study. The study is a completed double-blind RCT comparing nirsevimab versus palivizumab in children in their 1st and 2nd RSV season. For the present assessment, only the period of the 2nd RSV season is considered.

The relevant study population for the assessment exclusively comprises children in the 2nd RSV season with a history of bronchopulmonary dysplasia and/or a haemodynamically relevant congenital heart defect even during the 1st RSV season.

In the MEDLEY study, it was nevertheless not rechecked at the beginning of the 2nd RSV season whether the children still had the risk factors mentioned.

Overall, it therefore remains unclear to what extent the children in the MEDLEY study continued to have an increased risk of a severe course of RSV infection of the lower respiratory tract and thus an indication for secondary prevention with nirsevimab or palivizumab in their 2nd RSV season.

Therefore, no suitable data are available to assess the additional benefit of nirsevimab compared with the appropriate comparator therapy in children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is indicated. An additional benefit is therefore not proven.

b) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is not indicated

The G-BA determined the monitoring wait-and-see approach as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company cites the single-arm MUSIC study.

The patient population b) includes children with trisomy 21 (without bronchopulmonary dysplasia, without haemodynamically relevant heart defects). However, children with trisomy 21 were generally excluded from participation in the MUSIC study. Furthermore, the single-arm MUSIC study does not allow a comparison with the determined appropriate comparator therapy.

Therefore, no suitable data are available to assess the additional benefit of nirsevimab compared with the appropriate comparator therapy in children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is not indicated. An additional benefit is therefore not proven.

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

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

To determine the number of patients in the patient population a), the pharmaceutical company used 1.3% as an approximation of the number of those eligible for palivizumab in the 2nd RSV season. When transferring the percentage of children under 1 year of age (1st RSV season) to the starting basis (1-year-olds; 2nd RSV season), the pharmaceutical company assumed an overestimation, as children could have been administered palivizumab in the 1st RSV season due to their premature birth. According to the therapeutic information on RSV antibodies (Pharmaceuticals Directive Annex IV - Therapeutic information in accordance with Section 92, paragraph 2, sentence 7 SGB V), there is nevertheless no indication for secondary prevention for patients who have received palivizumab solely due to a premature birth for the 2nd RSV season.

In contrast, it is possible that not all patients with existing risk factors have also received palivizumab in practice. In addition, according to the pharmaceutical company, children with the risk factors of bronchopulmonary dysplasia and haemodynamically relevant congenital heart defects that existed during the 1st RSV season may experience an improvement in their health status, so that there is no longer an increased risk of a severe course of RSV infection

during the 2nd RSV season. Overall, the number of patients in the patient population a) stated by the pharmaceutical company tends to be overestimated.

The specification of the number of patients of patient population b) is an overestimation, assuming that only children with trisomy 21 without other risk factors are included in this patient population. This is due to the fact that the pharmaceutical company's estimate also includes children with immunodeficiency, neuromuscular diseases and cystic fibrosis.

For patient population b), an IQWiG estimate based on the percentage of children with trisomy 21 in 1-year-old children in Germany minus the percentage with the risk factors described is therefore considered more appropriate. This leads to a better approximation of the number of patients in the target population for patient population b), despite the persistence of uncertainty factors.

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 Beyfortus (active ingredient: nirsevimab) at the following publicly accessible link (last access: 13 February 2025):

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

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2025).

According to the product information for nirsevimab, children receive a 200 mg single dose. According to the product information, nirsevimab should be administered in children prior to the second RSV season.

The use of palivizumab is described in the therapeutic information from Annex IV to the Pharmaceuticals Directive,[1] which refers to the S2k guideline[2] "Guideline for the prevention of severe Respiratory Syncytial Virus (RSV) diseases in high-risk children". According to the therapeutic information, the use of palivizumab is most economical in children ≤ 24 months of age who are at high risk of severe courses of infection.

The use of palivizumab is limited to 5 months. The dosage is 15mg/kg BW. As the dosage in this particular patient group changes monthly within the 5 months due to weight gain, a range was formed for the lower limit when calculating the annual treatment costs for palivizumab. This results from the average body weight of a 12-month-old child at 9.69 kg[3] and the average body weight of a 15-month-old child at 10.43 kg[3]. For the upper limit, the data > 10 kg to 13.3 kg were used in accordance with the therapeutic information.

[1] https://www.g-ba.de/downloads/39-261-6264/2023-11-02_AM-RL-IV_TH-Palivizumab_BAnz.pdf
[2] https://register.awmf.org/assets/guidelines/048-012l_S2k_Prophylaxe-von-schweren-Erkrankungen-durch-Respiratory-Syncytial-Virus-RSV-bei-Risikokindern_2023-10.pdf
[3] Mean value over sex-specific medians (50th percentile) from Robert Koch Institute. Contributions to Federal Health Reporting: Reference percentiles for anthropometric measures and blood pressure from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) [online]. [Access: 17.12.2024]. URL: https://edoc.rki.de/bitstream/handle/176904/3254/28jWMa04ZjppM.pdf?sequence=1&isAllowed=y.b

Treatment period:

a) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is indicated

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Nirsevimab	Single dose	1	1	1
Appropriate comparator therapy				
Palivizumab	1 x monthly	5	1	5

b) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is not indicated

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Nirsevimab	Single dose	1	1	1
Appropriate comparator therapy				
Monitoring wait-and-see approach	Not calculable			

Consumption:

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

a) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is indicated

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Nirsevimab	100 mg	200 mg	2 x 100 mg	1	2 x 100 mg
Appropriate comparator therapy					
Palivizumab	Children 9.69 kg to 10.43 kg				
1st – 3rd administration (12th – 14th month)	15 mg/kg = 145.4 mg	145.4 mg	1 x 100 mg + 1 x 50 mg	3	3 x 100 mg + 3 x 50 mg
4th – 5th administration (15th – 16th month)	15 mg/kg = 156.5 mg	156.5 mg	2 x 100 mg	2	4 x 100 mg
1. – 5th administration	Children >10.1 kg to 13.3 kg				
	15 mg/kg = 199.5 mg	199.5 mg	2 x 100 mg	5	10 x 100 mg

b) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is not indicated

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Nirsevimab	100 mg	200 mg	2 x 100 mg	1	2 x 100 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				

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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

a) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is indicated

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					
Nirsevimab 100 mg	1 SFI	€ 453.83	€ 1.77	€ 24.50	€ 427.56
Appropriate comparator therapy					
Palivizumab 50 mg	1 SFI	€ 826.95	€ 1.77	€ 45.16	€ 780.02
Palivizumab 100 mg	1 SFI	€ 1,413.13	€ 1.77	€ 77.61	€ 1,333.75
Abbreviations: SFI = solution for injection					

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b) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is not indicated

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					
Nirsevimab 100 mg	1 SFI	€ 453.83	€ 1.77	€ 24.50	€ 427.56
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				
Abbreviations: SFI = solution for injection;					

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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 need to be taken into account.

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

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

Basic principles of the assessed medicinal product

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

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

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

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

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

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

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

<u>Concomitant active ingredient</u>

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

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the

date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

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

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

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

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

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

Designation

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

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

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the

combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

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

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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

Justification for the findings on designation in the present resolution:

a) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is indicated

   No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

   References:

   Product information for nirsevimab (Beyfortus); Beyfortus 50 mg/ 100 mg solution for injection in a pre-filled syringe; last revised: September 2024

b) Children during their 2nd RSV season up to 24 months of age with indication for secondary prevention of lower respiratory tract infections caused by RSV for whom palivizumab is not indicated

   No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

   References:

   Product information for nirsevimab (Beyfortus); Beyfortus 50 mg/ 100 mg solution for injection in a pre-filled syringe; last revised: September 2024

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 12 April 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place in the Subcommittee on Medicinal Products on 23 July 2024 once the positive opinion was granted.

On 15 August 2024, the pharmaceutical company submitted a dossier for the benefit assessment of nirsevimab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 15 August 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient nirsevimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 November 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 November 2024. The deadline for submitting statements was 6 December 2024.

The oral hearing was held on 6 January 2025.

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 11 February 2025, and the proposed draft resolution was approved.

At its session on 20 February 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	12 April 2022	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	23 July 2024	Examination of the appropriate comparator therapy
Working group Section 35a	18 December 2024	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	6 January 2025	Conduct of the oral hearing
Working group Section 35a	15 January 2025 5 February 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 February 2025	Concluding discussion of the draft resolution
Plenum	20 February 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 February 2025

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

Prof. Hecken