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 (secondary prevention of RSV infections, children during their 1st RSV season)

of 15 August 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of 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 31 May 2023, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for nirsevimab in the present therapeutic indication "Prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in children during their first RSV season" in accordance with Section 35a paragraph 5b SGB V.

At its session on 11 July 2023, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the other therapeutic indication covered by the application, at the latest six months after the first relevant date.

However, the marketing authorisation for the other therapeutic indication covered by the application according to Section 35a paragraph 5b SGB V was not granted within the 6-month period.

The pharmaceutical company therefore submitted a dossier in due time on 29 February 2024, i.e. six months after the first relevant date, in accordance with Section 4, paragraph 3, number 3 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure of the G-BA (VerfO) for the active ingredient nirsevimab with the therapeutic indication "Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 3 June 2024 on the G-BA website at (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of nirsevimab 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 nirsevimab.

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:

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 neonates and infants during their first RSV season.

Beyfortus should be used in accordance with official recommendations.

Therapeutic indication of the resolution (resolution of 15 August 2024):

Prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants with an indication for secondary prevention during their first RSV season.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

a) Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in whom palivizumab is indicated

Appropriate comparator therapy for nirsevimab:

Palivizumab

b) Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in 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 the therapeutic indication for the prevention of RSV-related lower respiratory tract infections in paediatric patients, the active ingredient palivizumab has been approved alongside nirsevimab.

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 are no resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. However, there is a therapeutic information for RSV antibodies (Pharmaceuticals Directive Annex IV - Therapeutic information pursuant to Section 92, paragraph 2, sentence 7 SGB V) dated 2 November 2023, which must be taken into account for both patient populations.

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

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

The present body of evidence includes the systematic reviews and Cochrane reviews 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,[2] the intervention is a secondary prevention for the following children: Children who required accompanying therapeutic measures for bronchopulmonary dysplasia within the last six months prior to the RSV season, children with haemodynamically relevant heart defects, children with trisomy 21 and children ≤ 6 months of age at the start of the RSV season who were born as preterm infants up to the 35th week of pregnancy (WOP) (34 (+6)).

In the overall assessment, a recommendation for targeted prevention with palivizumab can also be derived from the aggregated evidence for a) children with an indication for

2 Pharmaceuticals Directive/Annex IV

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.

In the absence of available options, monitoring wait-and-see approach is determined as the appropriate comparator therapy for nirsevimab for the prevention of lower respiratory tract disease caused by RSV in b) children with an indication for secondary prevention of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated. The therapeutic information on RSV antibodies (Pharmaceuticals Directive Annex IV - Therapeutic information pursuant to Section 92, paragraph 2, sentence 7 SGB V) of 2 November 2023 is also taken into account for patient population b).

No appropriate comparator therapy is determined for nirsevimab for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season, which is not secondary prevention, as this indication is currently not covered by the scope according to Section 35a SGB V.

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 with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in 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 MEDLEY study is a completed double-blind RCT comparing nirsevimab with palivizumab in children in their 1st year of life, in their first RSV season.

The study comprises a cohort of preterm infants and a cohort of children with a history of bronchopulmonary dysplasia or a haemodynamically relevant congenital heart defect.

According to the study protocol, children with a gestational age of ≤ 35 weeks who were eligible for palivizumab were enrolled in the cohort of preterm infants. Children in the cohort of preterm infants showed neither bronchopulmonary dysplasia nor a haemodynamically relevant congenital heart defect.

A total of 925 children were enrolled in the study; 615 children in the cohort of preterm infants and 310 children in the cohort with bronchopulmonary dysplasia or a haemodynamically relevant congenital heart defect. 616 children were randomised into the intervention arm and 309 children into the comparator arm. Randomisation was stratified according to the factors

region and age at entry into the first RSV season. The planned follow-up for all children was 360 days after the 1st dose (up to day 361).

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.

The dosage of nirsevimab and palivizumab was according to the product information.

The pharmaceutical company submitted results for the total population as well as for a sub-population. The evaluation of the sub-population comprised 245 children in the intervention arm and 118 children in the comparator arm. In the sub-population, the pharmaceutical company takes full account of the cohort with bronchopulmonary dysplasia or a haemodynamically relevant congenital heart defect and restricts the cohort of preterm infants to preterm infants born at a gestational age of < 29 weeks and ≤ 6 months of age at the start of the RSV season.

However, according to the current therapeutic information on RSV antibodies and the S2k guideline on the prevention of severe RSV diseases in high-risk infants, the indication for secondary prevention with palivizumab also exists for preterm infants ≤ 6 months of age at the start of their first RSV season and those born up to the completed 35th week of pregnancy (34 [+ 6 days]). Secondary prevention with palivizumab is therefore also indicated for these children, who are not included in the sub-population formed by the pharmaceutical company.

For the present benefit assessment, the results of the total population are therefore used. Although this also includes preterm infants who were > 6 months old at randomisation or who were born at a gestational age of > 35 weeks and for whom secondary prevention with palivizumab is therefore not indicated, the percentage in relation to the total population is only a maximum of 15%.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall mortality, there was no statistically significant difference between the treatment groups on day 361.

Morbidity

RSV-related lower respiratory tract infection

The endpoint of RSV-related lower respiratory tract infection is a composite endpoint. It comprises the components of RSV-related hospitalisation and RSV-related outpatient care.

The RSV-related hospitalisation subcomponent was defined as primary or nosocomial hospitalisation. Primary hospitalisation occurred in the event of hospital admission due to upper or lower respiratory tract infection and testing positive for RSV infection by reverse transcriptase polymerase chain reaction (RT-PCR) within 2 days before or after admission. A nosocomial hospitalisation occurred if a new deterioration in respiratory status was documented during a hospital stay and an RT-PCR-confirmed RSV infection was present. Children who were hospitalised due to an upper or lower respiratory tract infection had to have returned to baseline respiratory status or recovered from the respiratory illness before a new RSV infection was collected as a nosocomial hospitalisation.

The subcomponent RSV-related outpatient care is made up of the number of children who had to be treated in outpatient clinic, acute care and accident and emergency department due to an RSV infection.

Defined criteria had to be met for the hospitalisation and outpatient care components in order to collect an RSV-related lower respiratory tract infection. In addition to a medical examination, a positive RT-PCR test result for an RSV infection must also be present. In addition, at least one further criterion (cohort of preterm infants: increased respiratory rate, hypoxaemia or clinical signs of severe respiratory disease; children with bronchopulmonary dysplasia or a haemodynamically relevant congenital heart defect: increased respiratory rate, hypoxaemia, clinical signs of severe respiratory disease or prescription of new or a higher dose of existing medication compared to baseline) had to be fulfilled.

The operationalisation of both subcomponents is suitable. Therefore, the composite endpoint is used in its entirety for the benefit assessment.

The evaluations at the time point of day 151 represent a relevant evaluation time point against the background of the assessed therapeutic indication for prevention of RSV lower respiratory tract disease in children with an indication for secondary prevention during their first RSV season. An RSV season usually lasts around 5 months. Even taking into account the duration of action of the monoclonal antibodies stated in the product information and the approved use only during the RSV season, the evaluations on day 151 are used for the benefit assessment. This is supported by the statements made by the clinical experts during the oral hearing.

The evaluations on day 361 are also used for the benefit assessment since RSV-related lower respiratory tract infections still occurred to a relevant extent after the end of the 5-month RSV season and this data cut-off represents the longest available observation period.

It should also be noted that the MEDLEY study was conducted during the COVID-19 pandemic. Therefore, it cannot be ruled out that the general infection prevention measures also partially prevented RSV-related lower respiratory tract infections or that there were also relatively many RSV infections outside the season during this time and that a pandemic-associated shift in the RSV season took place.

For the composite endpoint of RSV-related lower respiratory tract infection, as well as for the individual components, there was no statistically significant difference between the treatment groups at the evaluation time points of day 151 and day 361.

Quality of life

Endpoints in the health-related quality of life category were not collected in the MEDLEY study.

Side effects

There was no statistically significant difference between the treatment groups for the endpoints of SAEs, severe AEs, and therapy discontinuation due to AEs on day 361.

Overall assessment

For the assessment of the additional benefit of nirsevimab in children with an indication for secondary prevention of lower respiratory tract infections caused by RSV in whom palivizumab is indicated, the pharmaceutical company presented the results of the MEDLEY study (comparison with palivizumab).

For the endpoint of overall mortality, there was no statistically significant difference between the treatment groups on day 361. In the morbidity category, there was also no statistically significant difference between the treatment groups at the evaluation time points of day 151 and day 361 for the composite endpoint of RSV-related lower respiratory tract infection. No data were submitted for the category of health-related quality of life. Likewise, in the side effects category, there was no statistically significant difference between the treatment groups.

In the overall assessment, an additional benefit of nirsevimab over the appropriate comparator therapy in children with an indication for secondary prevention of lower respiratory tract infections caused by RSV, for whom palivizumab is indicated, is therefore not proven.

b) Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in whom palivizumab is not indicated

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company submitted the results of the D5290C00003 and HARMONIE studies.

The D5290C00003 study is a completed, double-blind, randomised controlled trial comparing nirsevimab versus placebo for the prevention of RSV lower respiratory tract infections. For the present benefit assessment, the pharmaceutical company submitted the results of the final analysis on day 361.

Healthy preterm infants with a gestational age between 29 weeks of pregnancy + 0 days and 34 weeks of pregnancy + 6 days were enrolled. A total of 1,453 children were randomised in a ratio of 2:1. Randomisation was stratified by region and age at the time of randomisation. 969 children were enrolled in the nirsevimab arm and 484 children in the placebo arm.

In the D5290C00003 study, the sub-population of children with a body weight of less than 5 kg received an on-label dose of nirsevimab. This sub-population comprises 570 children in the nirsevimab arm and 290 children in the placebo arm.

Only healthy preterm infants in the 1st year of life with a gestational age between 29 weeks of pregnancy + 0 days and 34 weeks of pregnancy + 6 days were enrolled in the D5290C00003 study. Secondary prevention with palivizumab may be considered for these preterm infants in accordance with the therapeutic information on RSV antibodies, provided they are ≤ 6 months old at the start of their first RSV season.

Secondary prevention is no longer an option for preterm infants > 6 months of age. In the total study population, this affects 14.3% of the children enrolled.

The presented sub-population with a body weight of less than 5 kg at the time of randomisation, who were treated on-label with nirsevimab, therefore does not correspond to the G-BA-determined patient population b) of children for whom secondary prevention with palivizumab is not indicated.

Accordingly, the total population of the D5290C00003 study is also irrelevant, although some of the children received an off-label dose of nirsevimab.

The HARMONIE study is an ongoing, randomised, open-label, multicentre study investigating treatment with nirsevimab to prevent RSV-related hospitalisations compared to no intervention. Children ≤ 12 months of age and with a gestational age of at least 29 weeks of pregnancy were enrolled. Thus, both preterm infants and term infants were enrolled.

A total of 8,058 children were enrolled in the HARMONIE study and randomised in a 1:1 ratio (nirsevimab, N = 4,037 or no intervention, N = 4,021). Randomisation was stratified by country and age of the children. Treatment with nirsevimab was according to the product information.

The primary endpoint of the study is the RSV-related hospitalisation. Secondary endpoints include, among others, the endpoint of very severe RSV-related lower respiratory tract infections and endpoints on side effects.

The sub-population of the HARMONIE study presented by the pharmaceutical company for the benefit assessment also exclusively comprises preterm infants with a gestational age of 29 to 35 weeks of pregnancy. Around 20% of the children were already older than 6 months at the time of randomisation and therefore secondary prevention was not indicated for these children according to the current therapeutic information on RSV antibodies. For all preterm infants in the sub-population ≤ 6 months of age, on the contrary, there is not only an indication for secondary prevention according to the current therapeutic information on RSV antibodies, but they are also eligible for palivizumab treatment. The presented sub-population of the HARMONIE study therefore also does not correspond to the determined patient population b).

Thus, no suitable data are available for the assessment of the additional benefit of nirsevimab compared with the appropriate comparator therapy in children with an indication for secondary prevention of lower respiratory tract infections caused by RSV in whom palivizumab is not indicated. An additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Beyfortus with the active ingredient nirsevimab.

Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.

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

a) Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in whom palivizumab is indicated

b) Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in whom palivizumab is not indicated

On patient population a)

The Federal Joint Committee determined palivizumab as the appropriate comparator therapy.

For the assessment of the additional benefit, the pharmaceutical company presented the MEDLEY study. The MEDLEY study is a completed double-blind RCT comparing nirsevimab versus palivizumab in children in their 1st year of life, in their first RSV season.

In the endpoint categories of mortality, morbidity and side effects, there were no statistically significant differences between the treatment groups. No data were submitted for the category of health-related quality of life.

An additional benefit of nirsevimab over the appropriate comparator therapy in children with an indication for secondary prevention of lower respiratory tract infections caused by RSV, for whom palivizumab is indicated, is therefore not proven.

On patient population b)

The Federal Joint Committee determined the monitoring wait-and-see approach as the appropriate comparator therapy.

For the assessment of the additional benefit, the pharmaceutical company presented the D5290C00003 and HARMONIE studies.

The D5290C00003 study is a completed double-blind RCT comparing nirsevimab with placebo. Healthy preterm infants in the 1st year of life with a gestational age between 29 weeks + 0 days and 34 weeks + 6 days were enrolled in the study. However, secondary prevention with palivizumab may be considered for these children in accordance with the current therapeutic information on RSV antibodies, provided they are ≤ 6 months old at the start of the first RSV season. Secondary prevention is no longer an option for preterm infants > 6 months of age.

The HARMONIE study is an ongoing, randomised, open-label study comparing nirsevimab versus no intervention. The sub-population submitted by the pharmaceutical company includes preterm infants ≤ 6 months of age, who are not only eligible for secondary prevention but also suitable for palivizumab treatment according to the current therapeutic information on RSV antibodies.

The submitted sub-populations of the D5290C00003 and HARMONIE studies therefore do not correspond to the determined patient population b).

Thus, no suitable data are available for the assessment of the additional benefit of nirsevimab compared with the appropriate comparator therapy in children with an indication for secondary prevention of lower respiratory tract infections caused by RSV in 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).

The percentage value from the IQTiG (German Institute for Quality Assurance and Transparency in the Health Sector) national obstetrics evaluation as the lower limit, and the percentage value from the perinatal health report for Europe as the upper limit, refer to premature births at < 37 weeks of pregnancy. Since only preterm infants up to the 35th week of pregnancy (34 (+6 days) are included in the target population, it can therefore be assumed that too many cases were collected as a result. Furthermore, it remains unclear which birth months are not to be included in the calculation of preterm infants (age ≤ 6 months) due to the variation in the RSV season from year to year. This results in a potential overestimation.

The calculated percentage value of the lower limit only takes preterm infants into account. However, an overall uncertainty can be assumed despite the overestimated aspects of the lower limit described above since there is also an indication for secondary prevention for children with certain risk factors.

Assuming that only children with trisomy 21 without other risk factors are included in patient population b), the specification of the number of children is an overestimate. This is due to the fact that the pharmaceutical company's estimate includes children with

immunodeficiency, neuromuscular diseases and cystic fibrosis (example of severe lung diseases). Furthermore, the percentage of children with trisomy 21 and other risk factors who would have to be allocated to patient population a) remains unclear.

Overall, the lower limit of the patient population a) stated by the pharmaceutical company is to be classified as uncertain and the corresponding upper limit as overestimated. An overestimation can also be assumed for the range of the patient population b).

An IQWiG estimate based on the percentage of children with trisomy 21 in live births 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) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 8 August 2024):

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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2024).

According to the product information for nirsevimab, infants with a body weight < 5 kg receive a 50 mg single dose and infants with a body weight of ≥ 5 kg receive a 100 mg single dose. According to the product information, nirsevimab should be used in infants prior to the RSV season and in infants from birth or those born during the RSV season.

The use of palivizumab is described in the therapeutic information from Annex IV to the Pharmaceuticals Directive,[3] which refers to the S2k guideline[4] "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 at high risk of severe courses of infection ≤ 24 months of age and in children ≤ 6 months of age at the start of the RSV season who were born as preterm infants up to the completed 35th week of pregnancy (34+6 WOP).

The use of palivizumab is limited to 5 months. The dosage is 15mg/kg BW. As the dosage in this particular patient population changes monthly within the 5 months due to weight gain, the lower limit of ≥ 3.3 kg to 6.6 kg and the upper limit of > 10 kg to 13.3 kg were used to

3 https://www.g-ba.de/downloads/39-261-6264/2023-11-02_AM-RL-IV_TH-Palivizumab_BAnz.pdf
4 https://register.awmf.org/assets/guidelines/048-012l_S2k_Prophylaxe-von-schweren-Erkrankungen-durch-Respiratory-Syncytial-Virus-RSV-bei-Risikokindern_2023-10.pdf

calculate the annual treatment costs for palivizumab in accordance with the therapeutic information.

Treatment period:

a) Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in 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 with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in 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 with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in 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	Children < 5 kg				
	50 mg	50 mg	1 x 50 mg	1	1 x 50 mg
	Children > 5 kg				
	100 mg	100 mg	1 x 100 mg	1	1 x 100 mg
Appropriate comparator therapy					
Palivizumab 1st – 2nd administration up to 3.3 kg 3rd – 5th administration > 3.3 kg to 6.6 kg	Children ≤ 3.3 kg to 6.6 kg				
	15 mg/kg = 49.5 mg[5]	50 mg[6]	1 x 50 mg	2	2 x 50 mg +
	15 mg/kg = 99 mg	100 mg[6]	1 x 100 mg	3	3 x 100 mg
1st – 5th administration	Children >10 kg to 13.3 kg				
	15 mg/kg = 199.5 mg	200 mg[6]	2 x 100 mg	5	10 x 100 mg

b) <u>Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in whom palivizumab is not indicated</u>

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	Children < 5 kg				
	50 mg	50 mg	1 x 50 mg	1	1 x 50 mg
	Children > 5 kg				
	100 mg	100 mg	1 x 100 mg	1	1 x 100 mg

5 Children under 3.3 kg receive a partial amount of a 50 mg injection dose according to the product information
6 Intended for single use according to the product information.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
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 Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

a) Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in 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 50 mg	1 SFI	€ 453.83	€ 2.00	€ 24.50	€ 427.33
Nirsevimab 100 mg	1 SFI	€ 453.83	€ 2.00	€ 24.50	€ 427.33
Appropriate comparator therapy					
Palivizumab 50 mg	1 SFI	€ 826.95	€ 2.00	€ 45.16	€ 779.79
Palivizumab 100 mg	1 SFI	€ 1,413.13	€ 2.00	€ 77.61	€ 1,333.52
Abbreviations: SFI = solution for injection					

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b) Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in 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 50 mg	1 SFI	€ 453.83	€ 2.00	€ 24.50	€ 427.33
Nirsevimab 100 mg	1 SFI	€ 453.83	€ 2.00	€ 24.50	€ 427.33
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 information in the product information of the assessed medicinal product.

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

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

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

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

Designation

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

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

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

a) Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in 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 solution for injection in a pre-filled syringe; Beyfortus® 100 mg solution for injection in a prefilled syringe; last revised: April 2024

b) Children with an indication for secondary prevention of lower respiratory tract infections caused by Respiratory Syncytial Virus (RSV) in 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 solution for injection in a pre-filled syringe; Beyfortus® 100 mg solution for injection in a prefilled syringe; last revised: April 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. At its session on 12 December 2023, the Subcommittee on Medicinal Products conducted a review of the appropriate comparator therapy and specified it with regard to patient population b).

On 29 February 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 1, sentence 2 VerfO.

By letter dated 4 March 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 30 May 2024, and the written statement procedure was initiated with publication on the G-BA website on 3 June 2024. The deadline for submitting statements was 24 June 2024.

The oral hearing was held on 8 July 2024.

By letter dated 9 July 2024, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 23 July 2024.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 6 August 2024, and the proposed draft resolution was approved.

At its session on 15 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 April 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	12 December 2023	Examination of the appropriate comparator therapy and specification with regard to patient population b)
Working group Section 35a	3 July 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 July 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 July 2024 31 July 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	6 August 2024	Concluding discussion of the draft resolution
Plenum	15 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 August 2024

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

Prof. Hecken