Lumacaftor/ivacaftor (cystic fibrosis, 1 to < 2 years, F508del mutation, homozygous)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Lumacaftor/Ivacaftor (zystische Fibrose, 1 bis < 2 Jahre, F508del-Mutation, homozygot) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the Cystic Fibrosis Institute – a non-profit limited company for therapeutic research and development (Mukoviszidose Institut – gemeinnützige Gesellschaft für Forschung und Therapieentwicklung mbH) for participating in the written exchange and for their support. The respondent and the Cystic Fibrosis Institute – a non-profit limited company for therapeutic research and development were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator gene
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination lumacaftor/ivacaftor. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 12 July 2023.

Research question

The aim of the present report is to assess the added benefit of lumacaftor/ivacaftor in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in the treatment of cystic fibrosis (CF) in patients aged 1 to < 2 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of lumacaftor/ivacaftor

Therapeutic indication	**ACT**[a]
CF patients 1 to < 2 years of age who are homozygous for the F508del mutation in the CFTR gene	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the "Heilmittel Richtlinie", Remedies Directive] after exhausting all possible dietary measures).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of added benefit.

Results

Data presented by the company

VX16809/122 study

The VX16-809-122 study is a single-arm, open-label study of lumacaftor/ivacaftor in CF patients aged 1 to < 2 years who are homozygous for the F508del mutation in the CFTR gene. In the study, lumacaftor/ivacaftor granules were administered to a total of 46 children for

24 weeks (part B of the study) at a dose based on body weight as per Summary of Product Characteristics (SPC). The primary outcomes of the VX16-809-122 study (Part B) were the safety and tolerability of lumacaftor/ivacaftor, surveyed using adverse events, laboratory parameters, electrocardiograms, vital signs, pulse oximetry, and ophthalmological values. Secondary outcomes were sweat chloride concentration and pharmacokinetic parameters of lumacaftor/ivacaftor and its metabolites.

Company's argumentation regarding the transferability of added benefit from older patients to the patient population in the therapeutic indication

The company presents results from the single-arm study VX16-809-122 for the derivation of added benefit. Since the study is only a single-arm study, the company's arguments additionally refer to prior benefit assessments in older patients (≥ 2 years) within the present therapeutic indication. In the company's opinion, it is possible to transfer the results from older patients to children aged 1 to < 2 years and to use these results for deriving added benefit.

Assessment of the data presented by the company

Due to the lack of comparative data, the single-arm study VX16-809-122 presented by the company is unsuitable for assessing the added benefit of lumacaftor/ivacaftor compared with the ACT in CF patients aged 1 to < 2 years who are homozygous for the F508del mutation in the CFTR gene. The company's approach of transferring study results from older patients to the population of the present research question is plausible in view to the lack of comparative studies in children aged 1 to < 2 years. However, the implementation chosen by the company is unsuitable for this purpose due to insufficiently analysed data. A comparative analysis of the study data in the therapeutic indication in children aged 1 to 2 years versus the older age groups from which results are to be transferred is missing. This analysis should include, in particular, a comparative presentation of the study, intervention, and patient characteristics, including the patient-relevant outcomes recorded and the corresponding operationalizations as well as a comparative presentation of the results for all patient-relevant outcomes between the children in this therapeutic indication and particularly the 2- to 5-year-olds. A comparative analysis of the evidence on the ACT in the therapeutic indication of children aged 1 to 2 years, including information retrieval, is completely missing.

Results on added benefit

No suitable data are available for assessing the added benefit of lumacaftor/ivacaftor versus the ACT in CF patients aged 1 to < 2 years who are homozygous for the F508del mutation in the CFTR gene. This results in no hint of an added benefit of lumacaftor/ivacaftor in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of lumacaftor/ivacaftor.

Table 3: Lumacaftor/ivacaftor – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
CF patients 1 to < 2 years of age who are homozygous for the F508del mutation in the CFTR gene	BSC[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the "Heilmittel Richtlinie", Remedies Directive] after exhausting all possible dietary measures).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of the present report is to assess the added benefit of lumacaftor/ivacaftor in comparison with BSC as the ACT in the treatment of CF in patients aged 1 to < 2 years who are homozygous for the F508del mutation in the CFTR gene.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of lumacaftor/ivacaftor

Therapeutic indication	**ACT**[a]
CF patients 1 to < 2 years of age who are homozygous for the F508del mutation in the CFTR gene	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the "Heilmittel Richtlinie", Remedies Directive] after exhausting all possible dietary measures).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on lumacaftor/ivacaftor (status: 24 April 2023)
- bibliographical literature search on lumacaftor/ivacaftor (last search on 25 April 2023)
- search in trial registries / trial results databases for studies on lumacaftor/ivacaftor (last search on 20 April 2023)
- search on the G-BA website for lumacaftor/ivacaftor (last search on 20 April 2023)

To check the completeness of the study pool:

- search in trial registries for lumacaftor/ivacaftor (last search on 31 July 2023); see I Appendix A of the full dossier assessment for search strategies

Concurring with the company, the check of the completeness of the study pool identified no randomized controlled trials (RCTs) for the comparison of lumacaftor/ivacaftor versus the ACT of BSC in the present therapeutic indication.

Due to the lack of directly comparative studies versus the ACT, the company additionally conducted an information retrieval on nonrandomized studies for the intervention and thereby identified the single-arm study VX16-809-122 [3] (see following section). The company has conducted no information retrieval for the ACT. To derive added benefit, the company sought to transfer study results from older patient groups in the therapeutic indication to the population of children aged 1 to < 2 years, which is relevant for the benefit assessment.

The data presented by the company are unsuitable for deriving conclusions on the added benefit of lumacaftor/ivacaftor in comparison with the ACT in CF patients aged 1 to < 2 years who are homozygous for the F508del mutation in the CFTR gene. A detailed rationale is provided below.

I 3.1 Data presented by the company

VX16809/122 study

The VX16-809-122 study is a single-arm, open-label study of lumacaftor/ivacaftor in CF patients aged 1 to < 2 years who are homozygous for the F508del mutation in the CFTR gene. As per inclusion criteria, beyond the presence of the mutation, patients had to exhibit either (i) a sweat chloride concentration ≥ 60 mmol/l and/or (ii) chronic sinopulmonary disease or gastrointestinal/nutritional abnormality. The study was conducted in 2 parts (Part A and

Part B). The duration of treatment was only 15 days in Part A of the study and 24 weeks in Part B. Due to the short treatment duration in Part A of the study (< 24 weeks), the company took into account only Part B for the benefit assessment. In Part B of the study, lumacaftor/ivacaftor granules were administered to a total of 46 children at a dose based on body weight as per SPC [4]. The 24-week treatment phase was followed by a 2-week washout phase with subsequent safety follow-up visit. Patients then had the opportunity to participate in a single-arm extension study (study VX19-809-124 [5]). According to the company, results of the extension study are not yet available. The primary outcomes of the VX16-809-122 study (Part B) were the safety and tolerability of lumacaftor/ivacaftor, surveyed using adverse events, laboratory parameters, electrocardiograms, vital signs, pulse oximetry, and ophthalmological values. Secondary outcomes were sweat chloride concentration and pharmacokinetic parameters of lumacaftor/ivacaftor and its metabolites.

Company reasoning on transferability

The company presents results from the single-arm study VX16-809-122 in children from 1 to < 2 years of age for the derivation of added benefit in the present therapeutic indication. Since the study is only a single-arm study, the company's reasoning on added benefit additionally refers to earlier benefit assessments in older patients in the present therapeutic indication (2-5 years [6-9], 6 to < 12 years [10,11], ≥ 12 years [12,13]). In the company's opinion, it is possible to transfer the results from older patients to children aged 1 to < 2 years and to use these results for deriving added benefit. The company justifies this view with what it deems to be a similar mode of action of lumacaftor/ivacaftor in different age groups, the comparable course of disease in patients with the same mutation, and similar clinical effects with regard to effectiveness and safety in the different age groups. In addition, the company deems the decisive criterion for transfer to be that the ACT of BSC is identical for all age groups > 1 year. In the benefit assessments in patients aged 12 years and older, the G-BA had derived an indication of considerable added benefit on the basis of 2 RCTs, and for both patients aged 6 to 11 years and 2 to 5 years, an indication of a non-quantifiable added benefit on the basis of 1 RCT each, taking into account evidence from the older age groups.

Furthermore, the company included a model on survival time [14] in its arguments for deriving added benefit without describing it in more detail in Module 4 A. In its opinion, this model shows longer survival for patients starting lumacaftor/ivacaftor treatment from age 2 years.

Overall, the company claims a hint of nonquantifiable added benefit based on the overall analysis of the available evidence.

I 3.2 Assessment of the data presented by the company

The data presented by the company are unsuitable for assessing the benefit of lumacaftor/ivacaftor in comparison with the ACT. This is explained below.

No conclusions on added benefit are possible on the basis of the VX16-809-122 study

Due to the lack of comparative data, the single-arm study VX16-809-122 presented by the company is unsuitable for assessing the added benefit of lumacaftor/ivacaftor compared with the ACT in CF patients aged 1 to < 2 years who are homozygous for the F508del mutation in the CFTR gene.

Insufficient analysis for the transfer of evidence from children aged ≥ 2 years to the target population of children aged 1 to < 2 years

The company's approach of transferring study results from older patients to the population of the present research question is plausible in view to the lack of comparative studies in children aged 1 to < 2 years. However, the implementation chosen by the company is unsuitable for this purpose due to insufficiently analysed data. An added benefit of lumacaftor/ivacaftor compared with the ACT in CF patients aged 1 to < 2 years who are homozygous for the F508del mutation in the CFTR gene cannot be derived from the data presented by the company for the following reasons:

- A comparative analysis of the study data in the therapeutic indication in children aged 1 to 2 years versus the older age groups from which results are to be transferred is missing. This includes in particular
  - the comparative presentation of the study, intervention, and patient characteristics as well as the patient-relevant outcomes surveyed, including corresponding operationalizations. The company has not presented such a comparison for the benefit assessment.
  - the comparative presentation of the results for all patient-relevant outcomes between the children in this therapeutic indication and in particular the children aged 2 to 5 years. The company makes such a comparison only in text form and mentions only individual results for the intervention arm of the older children. A comparative analysis of the evidence on the ACT in the therapeutic indication of children aged 1 to 2 years, including information retrieval, is completely missing.
- The modelling of survival time mentioned by the company is subject to major uncertainties and is unsuitable for the present benefit assessment, as already described in benefit assessment A21-122 in children aged 2 to 5 years [15].
- Cystic fibrosis is a progressive disease; therefore, the greater the age difference between the population to be analysed and the population from which the transfer is to be made, the more questionable is the transferability of data. For the analysis and discussion of transferability, the primary population to be used here should be children aged 2 to 5 years because comparative evidence from 1 RCT is already available for this

population. In the RCT available for this age group, the corresponding benefit assessment A21-122 showed neither favourable nor unfavourable effects [15].

Conclusion

Overall, the data presented by the company are unsuitable for drawing conclusions on the added benefit of lumacaftor/ivacaftor in comparison with the ACT. The European Medicines Agency (EMA) likewise notes at various points in the European Public Assessment Report (EPAR) of the marketing authorization extension [16] that insufficient clinical evidence is available to date for children aged 1 to < 2 years and therefore instructs the company to collect comparative evidence in this therapeutic indication after approval as part of a post-authorization efficacy study (PAES). The corresponding study protocol was to be submitted by June 2023, with the final report expected in December 2025.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of lumacaftor/ivacaftor versus the ACT in CF patients aged 1 to < 2 years who are homozygous for the F508del mutation in the CFTR gene. This results in no hint of an added benefit of lumacaftor/ivacaftor in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of lumacaftor/ivacaftor in comparison with the ACT is summarized in Table 5.

Table 5: Lumacaftor/ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients 1 to < 2 years of age who are homozygous for the F508del mutation in the CFTR gene	BSC[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the "Heilmittel Richtlinie", Remedies Directive] after exhausting all possible dietary measures).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The assessment described above deviates from the assessment by the company, which derived a hint for nonquantifiable added benefit based on the data of the single-arm study as well as the transfer of results from patients ≥ 2 years to the target population of children aged 1 to < 2 years.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Rayment JH, Asfour F, Rosenfeld M et al. A Phase 3, Open-Label Study of Lumacaftor/Ivacaftor in Children 1 to Less Than 2 Years of Age With Cystic Fibrosis Homozygous for F508del-CFTR. Am J Respir Crit Care Med 2022. https://dx.doi.org/10.1164/rccm.202204-0734OC.

4. Vertex. Orkambi 75 mg/94 mg /-100 mg/125 mg /-150 mg/188 mg Granulat im Beutel [online]. 2023 [Accessed: 17.08.2023]. URL: https://www.fachinfo.de.

5. Vertex Pharmaceuticals. Long-term Safety of Lumacaftor/Ivacaftor in Subjects With Cystic Fibrosis Who Are Homozygous for F508del and 12 to <24 Months of Age at Treatment Initiation [online]. 2022 [Accessed: 17.08.2023]. URL: https://classic.clinicaltrials.gov/show/NCT04235140.

6. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V) - Lumacaftor/Ivacaftor (Neubewertung nach Fristablauf: zystische Fibrose, homozygot F508del-Mutation im CFTR-Gen, ≥ 2 bis 5 Jahre) [online]. 2022 [Accessed: 28.04.2023]. URL: https://www.g-ba.de/downloads/40-268-8361/2022-03-18_AM-RL-XII_Lumacaftor-Ivacaftor_D-733_TrG.pdf.

7. Vertex Pharmaceuticals. Dossier zur Nutzenbewertung gemäß § 35a SGB V - Lumacaftor/Ivacaftor (Orkambi) - Modul 4 A - Behandlung der zystischen Fibrose bei Patienten von 2 bis 5 Jahren, die homozygot bezüglich der F508del-Mutation im CFTR-Gen sind - Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen - 27. September. 2021.

8. Stahl M, Roehmel J, Eichinger M et al. Effects of Lumacaftor/Ivacaftor on Cystic Fibrosis Disease Progression in Children 2 through 5 Years of Age Homozygous for F508del-CFTR: A Phase 2 Placebo-controlled Clinical Trial. Ann Am Thorac Soc 2023. https://dx.doi.org/10.1513/AnnalsATS.202208-684OC.

9. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Lumacaftor/Ivacaftor (neues Anwendungsgebiet: zystische Fibrose, Patienten 2-5 Jahre) [online]. 2019 [Accessed: 07.04.2023]. URL: https://www.g-ba.de/downloads/40-268-5938/2019-08-15_AM-RL-XII_Lumacaftor-Ivacaftor_D-432_TrG.pdf.

10. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Lumacaftor/Ivacaftor (neues Anwendungsgebiet: Behandlung der zystischen Fibrose (CF, Mukoviszidose) bei Patienten ab 6 Jahren, die homozygot für die F508del-Mutation im CFTR-Gen sind) [online]. 2018 [Accessed: 07.04.2023]. URL: https://www.g-ba.de/downloads/40-268-5174/2018-08-02_AM-RL-XII_Lumacaftor-Ivacaftor_D-339_TrG.pdf.

11. Vertex Pharmaceuticals. Dossier zur Nutzenbewertung gemäß § 35a SGB V - Lumacaftor/Ivacaftor (Orkambi) - Modul 4 A - Behandlung der zystischen Fibrose bei Patienten im Alter von 6 bis 11 Jahren, die homozygot bezüglich der F508del-Mutation im CFTR-Gen sind - Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen. 30. Januar. 2018.

12. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Lumacaftor/Ivacaftor [online]. 2016 [Accessed: 28.04.2023]. URL: https://www.g-ba.de/downloads/40-268-3799/2016-06-02_AM-RL-XII_Lumacaftor-Ivacaftor_D-204_TrG.pdf.

13. Vertex Pharmaceuticals. Dossier zur Nutzenbewertung gemäß § 35a SGB V - Lumacaftor/Ivacaftor (Orkambi) - Modul 4 A - Behandlung der zystischen Fibrose bei Patienten ab 12 Jahren, die homozygot bezüglich der F508del-Mutation im CFTR-Gen sind - Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen. 10. Dezember. 2015.

14. Iqvia. Analysis of predicted survival in CF patients homozygous for the F508del mutation treated with Orkambi for Germany, Version 2.0. 2021.

15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Lumacaftor/Ivacaftor (zystische Fibrose, 2 bis 5 Jahre, F508del-Mutation, homozygot) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung [online]. 2021 [Accessed: 28.08.2023]. URL: https://www.iqwig.de/download/a21-122_lumacaftor-ivacaftor_nutzenbewertung-35a-sgb-v_v1-0.pdf.

16. European Medicines Agency. Orkambi; Assessment report [online]. 2023 [Accessed: 17.08.2023]. URL: https://www.ema.europa.eu/documents/variation-report/orkambi-h-c-3954-x-0078-g-epar-assessment-report-extension_en.pdf.

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