Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis, 2 to 5 years, F508del mutation, MF mutation, heterozygous)

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

EXTRACT

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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 Mukoviszidose e. V. (Cystic Fibrosis Institute) for participating in the written exchange and for their support. The respondent and the Mukoviszidose e. V. 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
CFTR	cystic fibrosis transmembrane conductance regulator
ELX	elexacaftor
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IVA	ivacaftor
MF	minimal function
PAES	post-approval efficacy study
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristic

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 ivacaftor/tezacaftor/elexacaftor (in combination with 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 5 December 2023.

Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as "ivacaftor/tezacaftor/elexacaftor + ivacaftor") in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in cystic fibrosis patients 2 to 5 years of age who are heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and have a minimal function (MF) mutation on the second allele.

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 ivacaftor/tezacaftor/elexacaftor + ivacaftor

Therapeutic indication	**ACT[a]**
Patients with cystic fibrosis from 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the 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 German Remedies Directive] under exhaustion of all possible dietary interventions).

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

The company designated BSC as the ACT, thus following the G-BA's specification.

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

The check of completeness of the study pool produced no randomized controlled trials (RCTs) for a direct comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT BSC in

the present therapeutic indication. Due to the lack of studies of direct comparison, the company additionally conducted an information retrieval for non-comparative studies with the intervention and identified the single-arm study VX20-445-111 and its extension study VX20-445-112. For its assessment of the added benefit, the company primarily used the results of study VX20-445-111. Furthermore, the company sought to transfer study results from older patient groups in the therapeutic indication to the population of children aged 2 to 5 years, which is relevant for the benefit assessment. The company conducted no information retrieval on the ACT, however.

Data presented by the company

Study VX20-445-111 and associated extension study VX20-445-112

Study VX20-445-111 is a single-arm, open-label study investigating treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor in cystic fibrosis patients from 2 to 5 years of age. The study included patients who were either homozygous for the F508del mutation in the CFTR gene or heterozygous for the F508del mutation in the CFTR gene and had an MF mutation on the second allele (hereinafter referred to as "F508del/MF mutation"). In the study, a total of 52 children of the present research question (F508del/MF mutation) were treated with ivacaftor/tezacaftor/elexacaftor granules in combination with ivacaftor granules at a dosage based on body weight and in compliance with the Summary of Product Characteristics (SPC) (Part B of the study). Following the 24-week treatment in Part B of study VX20-445-111, patients had the opportunity to participate in a single-arm extension study (study VX20-445-112), where treatment was continued for a period of up to a further 192 weeks. The primary outcome of Part B of study VX20-445-111 and study VX20-445-112 was the assessment of safety and tolerability based on adverse events as well as laboratory and vital parameters. Further outcomes included pulmonary exacerbations, growth parameters, sweat chloride, lung clearance index$_{2.5}$, and other laboratory parameters.

For its benefit assessment, the company primarily used results from Part B of study VX20-445-111 on the subpopulation of patients with F508del/MF mutation and additionally presented results of an interim analysis of study VX20-445-112 after 48 weeks of treatment (corresponding overall to treatment week 72) for the entire study population irrespective of the underlying mutation type.

Company reasoning on transferability

In addition to the results of studies VX20-445-111 and VX20-445-112, the company considered further studies conducted by the company in older age groups in the therapeutic indication, and used these studies for its reasoning in the derivation of the added benefit. To this end, the company referred to previous benefit assessments of ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients of different age groups with F508del/MF mutation (6 to 11 years, 12 years and older), in particular to results from the studies VX19-445-116 (6 to 11 years) and

VX17-445-102 (12 years and older), as it assumed that the results were transferable to patients aged 2 to 5 years with the same type of mutation.

Data presented by the company are unsuitable for the benefit assessment

The primary study used by the company to derive added benefit, VX20-445-111, and its extension study VX20-445-112, are each single-arm studies, which do not allow any comparison with the ACT. Hence, these studies are unsuitable for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in cystic fibrosis patients aged 2 to 5 years with F508del/MF mutation.

Due to the lack of studies of direct comparison in children between 2 and 5 years of age, the company's approach of transferring study results from older patients to the population of the present research question is comprehensible. However, the dossier does not include any studies or other information for evaluating the course of disease under the ACT, BSC, for the population of the present research question. Due to the lack of comparative data, the company's reasoning on transferring added benefit between different age groups is thus based exclusively on the comparison of results on treatment with the intervention. In addition, it remains unclear whether data on treatment with BSC are available for the age group of the present research question, which the company could have evaluated for a comparison in the present therapeutic indication.

If corresponding data on the ACT from non-comparative studies are available, a complete comparison of all data on the intervention and comparator side for the different age groups relevant for a transfer of the results would be necessary to be able to assess whether a transfer is possible. However, the company did not conduct any information retrieval on non-comparative studies with the ACT. For the older age groups in the present therapeutic indication, the company also did not present any evaluated data on the relevant studies for the transfer. A comprehensive evaluation of all results on intervention and comparator therapy relevant for the transfer is therefore not available either for the age group of the present research question or for the older age groups. The inadequately evaluated data presented by the company are therefore not suitable overall for transferring the results of the older patients to the younger age group.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + 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 shows a summary of the probability and extent of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor.

Table 3: Ivacaftor/tezacaftor/elexacaftor + ivacaftor – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients with cystic fibrosis from 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele	BSC[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the 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 German Remedies Directive] under exhaustion of all possible dietary interventions).

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

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 this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as "ivacaftor/tezacaftor/elexacaftor + ivacaftor") in comparison with BSC as the ACT in cystic fibrosis patients 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele.

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 ivacaftor/tezacaftor/elexacaftor + ivacaftor

Therapeutic indication	**ACT**[a]
Patients with cystic fibrosis from 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the 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 German Remedies Directive] under exhaustion of all possible dietary interventions).

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

The company designated BSC as the ACT, thus following the G-BA's specification. According to the company, all cystic fibrosis patients were to receive individualized treatment for the alleviation of symptoms and improvement of quality of life, in addition to treatment with CFTR modulators. This is appropriate.

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 lists on ivacaftor/tezacaftor/elexacaftor + ivacaftor (status: 15 September 2023)
- bibliographic literature search for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 5 September 2023)
- search in trial registries/trial results databases for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 5 September 2023)
- search on the G-BA website for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 5 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 18 December 2023); see I Appendix A of the full dossier assessment for the search strategies

Concurring with the company, the check of the completeness of the study pool produced no RCT on the direct comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT BSC in the present therapeutic indication.

Due to the lack of studies of direct comparison, the company additionally conducted an information retrieval for non-comparative studies with the intervention and identified the single-arm study VX20-445-111 [3] and its extension study VX20-445-112 [4]. The company conducted no information retrieval for the ACT. For its assessment of the added benefit, the company primarily used the results of study VX20-445-111. Furthermore, the company sought to transfer study results from older patient groups in the therapeutic indication to the population of children aged 2 to 5 years, which is relevant for the benefit assessment.

The data presented by the company are unsuitable for drawing any conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT for the population of the present research question. A detailed rationale is provided below.

Data presented by the company

Study VX20-445-111 and associated extension study VX20-445-112

Study VX20-445-111 is a single-arm, open-label study investigating treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor in cystic fibrosis patients from 2 to 5 years of age. The study included patients who were either homozygous for the F508del mutation in the

CFTR gene or heterozygous for the F508del mutation in the CFTR gene and had an MF mutation on the second allele (hereinafter referred to as “F508del/MF mutation”). According to the inclusion criteria, patients had to have a stable disease at the start of treatment.

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. The company only considered Part B for the benefit assessment. In Part B of the study, a total of 52 children of the present research question (F508del/MF mutation) were treated with ivacaftor/tezacaftor/elexacaftor granules in combination with ivacaftor granules at a dosage based on body weight and in compliance with the SPC [5]. Following the 24-week treatment phase, patients had the opportunity to participate in a single-arm extension study (study VX20-445-112), where treatment was continued for a period of up to another 192 weeks. Patients who had reached the age of 6 years during the extension study received the study medication, if possible, in tablet form in a dosage based on body weight in compliance with the SPC [6]. At the time of the benefit assessment, results of Part B of study VX20-445-111 after 24 weeks of treatment and results of an interim analysis of study VX20-445-112 after 48 weeks of treatment (corresponding overall to treatment week 72) were available.

The primary outcome of Part B of study VX20-445-111 and study VX20-445-112 was the assessment of safety and tolerability based on adverse events as well as laboratory and vital parameters. Further outcomes included pulmonary exacerbations, growth parameters, sweat chloride, lung clearance index$_{2.5}$, and other laboratory parameters.

For its benefit assessment, the company primarily used results from Part B of study VX20-445-111 on the subpopulation of patients with F508del/MF mutation and additionally presented results of the interim analysis of study VX20-445-112 for the entire study population irrespective of the underlying mutation type.

Company reasoning on transferability

In addition to the results of studies VX20-445-111 and VX20-445-112, the company considered further studies conducted by the company in older age groups in the therapeutic indication, and used these studies for its reasoning in the derivation of the added benefit. To this end, the company referred to previous benefit assessments of ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients of different age groups with F508del/MF mutation (6 to 11 years [7], 12 years and older [8]), as it assumed that the results were transferable to patients aged 2 to 5 years with the same type of mutation.

The company reasoned that results were transferable due to a mechanism of action it deemed comparable, the clinical picture of the disease, and sufficiently similar results found in patients from the different age groups. However, the company mentioned results from the studies in older age groups for the RCTs VX19-445-116 (6 to 11 years [9]) and VX17-445-102 (12 years

and older [10]) only in its reasoning to derive the added benefit, referring to the associated procedures for benefit assessment in the respective age groups. RCT VX19-445-116 was subject of the dossier assessment for Commissions A22-15 and A22-21 [11], RCT VX17-445-102 was subject of the dossier assessment for Commission A20-83 [12].

In addition to the RCTs from benefit assessment procedures in the older age groups, the company's reasoning also referred to the results of the single-arm VX18-445-106 study [13], which included patients aged 6 to 11 years who were either homozygous for the F508del mutation in the CFTR gene or heterozygous for the F508del mutation in the CFTR gene and had an MF mutation on the second allele. However, the company did not address the results of this study in its reasoning.

Data presented by the company are unsuitable for the benefit assessment

The data presented by the company are unsuitable for assessing the benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT. This is justified below.

Single-arm studies unsuitable for the benefit assessment

The primary study used by the company to derive added benefit, VX20-445-111, and its extension study VX20-445-112, are each single-arm studies, which do not allow any comparison with the ACT. Hence, these studies are unsuitable for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in cystic fibrosis patients aged 2 to 5 years with F508del/MF mutation.

Transfer of results from older patients (6 to 11 years and ≥ 12 years) to the target population unsuitable

The company's approach of transferring study results from older patients to the population of the present research question is plausible in view of the lack of studies of direct comparison in children aged 2 to 5 years. However, the implementation of the company is not suitable for the following reasons.

The company provided no information retrieval for non-comparative studies for the ACT. Thus, the dossier also does not include any studies or other information for evaluating the course of disease under the ACT, BSC, for the population of the present research question. Due to the lack of comparative data, the company's reasoning on transferring added benefit between different age groups is thus based exclusively on the comparison of results on treatment with the intervention. According to comments made by clinicians during the oral hearing on the early benefit assessment procedure for lumacaftor/ivacaftor [14] (dossier assessment for Commission A23-72 [15]), it also remains unclear whether there are data on

treatment with BSC for the age group of the present research question, which the company could have evaluated for a comparison in the present therapeutic indication.

If corresponding data on the ACT from non-comparative studies are available, a complete comparison of all data on the intervention and comparator side for the different age groups relevant for a transfer of the results would be necessary to be able to assess whether a transfer is possible. However, the company did not conduct any information retrieval on non-comparative studies with the ACT. For the older age groups in the present therapeutic indication, the company also did not present any evaluated data on the relevant studies for the transfer. In its reasoning, it only cited results in text form from 2 selected studies conducted by the company in the older age groups. A comprehensive evaluation of all results on intervention and comparator therapy relevant for the transfer is therefore not available either for the age group of the present research question or for the older age groups. The inadequately evaluated data presented by the company are therefore not suitable overall for transferring the results of the older patients to the younger age group.

For pulmonary exacerbations, the key outcome in the present therapeutic indication, the dossier assessment of the adjacent age group (6 to 11 years) showed positive effects of ivacaftor/tezacaftor/elexacaftor + ivacaftor [11]. However, the company itself pointed out in its reasoning that, due to different observation periods and operationalizations of the outcome in the underlying studies, a comparison of the frequency of the occurrence of pulmonary exacerbations between the different age groups is not meaningful.

Conclusion

In summary, the data presented by the company are unsuitable to derive conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT for cystic fibrosis patients aged 2 to 5 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele.

The European Medicines Agency (EMA) also noted in the context of the extension of approval [16] that the data situation for patients aged 2 to 5 years who are heterozygous for the F508del mutation in the CFTR gene is insufficient and that there are uncertainties regarding the optimal age to start treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor. The company was therefore requested by the EMA to collect comparative evidence for patients aged 2 to 5 years with heterozygous F508del mutation in the CFTR gene as part of a post-approval efficacy study (PAES). The corresponding study protocol is to be submitted by June 2024, with the final report expected in December 2029 [16].

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT in cystic fibrosis patients aged 2 to 5 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele. There is no hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT.

Table 5: Ivacaftor/tezacaftor/elexacaftor + ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Patients with cystic fibrosis from 2 to 5 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the second allele	BSC[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the 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 German Remedies Directive] under exhaustion of all possible dietary interventions).

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

The assessment described above deviates from the assessment by the company, which derived a hint of major added benefit based on the data of the single-arm VX20-445-111 study as well as the transfer of results from patients aged 6 to 11 years, and 12 years and older, to the target population of children aged 2 to 5 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 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.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://doi.org/10.1002/bimj.201300274.

3. Goralski JL, Hoppe JE, Mall MA et al. Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2-5 Years with Cystic Fibrosis and at Least One F508del Allele. Am J Respir Crit Care Med 2023; 208(1): 59-67. https://doi.org/10.1164/rccm.202301-0084OC.

4. Vertex Pharmaceuticals. Evaluation of Long-term Safety and Efficacy of ELX/TEZ/IVA in Cystic Fibrosis (CF) Participants 2 Years and Older [online]. 2023 [Accessed: 09.01.2024]. URL: https://clinicaltrials.gov/study/NCT05153317.

5. Vertex. Kaftrio 60 mg/40 mg/80 mg/-75 mg/50 mg/100 mg Granulat im Beutel [online]. 2023 [Accessed: 05.12.2023]. URL: https://www.fachinfo.de.

6. Vertex. Kaftrio 37,5 mg/25 mg/50 mg/-75 mg/50 mg/100 mg Filmtabletten [online]. 2023 [Accessed: 02.01.2024]. URL: https://www.fachinfo.de.

7. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Ivacaftor / Tezacaftor / Elexacaftor (Neues Anwendungsgebiet: Zystische Fibrose, Kombinationsbehandlung mit Ivacaftor, ab 6 bis ≤ 11 Jahre (heterozygot bzgl. F508del- und MF-Mutation)) [online]. 2022 [Accessed: 23.01.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/793/.

8. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Ivacaftor/Tezacaftor/Elexacaftor (Zystische Fibrose, Kombinationsbehandlung mit Ivacaftor bei Patienten ab 12 Jahren (heterozygot bzgl. F508del und MF-Mutation)) [online]. 2020 [Accessed: 29.01.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/583/.

9. Vertex Pharmaceuticals. A Study Evaluating Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis and F/MF Genotypes [online]. 2021 [Accessed: 15.03.2022]. URL: https://ClinicalTrials.gov/show/NCT04353817.

10. Middleton PG, Mall MA, Drevinek P et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med 2019; 381(19): 1809-1819. https://doi.org/10.1056/NEJMoa1908639.

11. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ivacaftor/Tezacaftor/Elexacaftor und Ivacaftor (zystische Fibrose, 6 bis 11 Jahre, F508del-Mutation, MF-Mutation, heterozygot) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a22-15-und-a22-21_ivacaftor-tezacaftor-elexacaftor-und-ivacaftor_nutzenbewertung-35a-sgb-v_v1-0.pdf.

12. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ivacaftor (Kombination mit Ivacaftor/Tezacaftor/Elexacaftor; zystische Fibrose, ab 12 Jahre, F508del-Mutation, MF-Mutation, heterozygot) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a20-83_ivacaftor_nutzenbewertung-35a-sgb-v_v1-0.pdf.

13. Zemanick ET, Taylor-Cousar JL, Davies J et al. A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. Am J Respir Crit Care Med 2021; 203(12): 1522-1532. https://doi.org/10.1164/rccm.202102-0509OC.

14. Gemeinsamer Bundesausschuss. Lumacaftor/Ivacaftor; mündliche Anhörung gemäß § 35 a Abs. 2 SGB V; stenografisches Wortprotokoll [online]. 2023 [Accessed: 11.12.2023]. URL: https://www.g-ba.de/downloads/91-1031-974/2023-11-27_Wortprotokoll_Lumacaftor-Ivacaftor_D-947.pdf.

15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Lumacaftor/Ivacaftor (zystische Fibrose, 1 bis < 2 Jahre, F508del-Mutation, homozygot); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 16.10.2023]. URL: https://doi.org/10.60584/A23-72.

16. European Medicines Agency. Kaftrio; Assessment report [online]. 2023 [Accessed: 29.01.2024]. URL: https://www.ema.europa.eu/en/documents/variation-report/kaftrio-h-c-005269-x-0033-epar-assessment-report-variation_en.pdf.

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