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 Ivacaftor (new therapeutic indication: cystic fibrosis, combination regimen Ivacaftor/ Tezacaftor/ Elexacaftor, 6 to 11 years (heterozygous for F508del and gating mutations (including R117H))

of 4 August 2022

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 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 ivacaftor (Kalydeco) was listed for the first time on 15 August 2012 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

Ivacaftor is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

Within the previously approved therapeutic indications, the sales volume of ivacaftor with the statutory health insurance at pharmacy sales price including value-added tax exceeded € 50 million. Evidence must therefore be provided for ivacaftor in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 7 January 2022, Kalydeco received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 3 February 2022, i.e. no later than four weeks after the pharmaceutical company has been notified of the authorisation for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient ivacaftor with the new therapeutic indication (cystic fibrosis, combination regimen with ivacaftor/ tezacaftor/ elexacaftor, 6 to 11 years (heterozygous for the F508del mutation and carry a gating mutation on the second allele).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 16 May 2022, 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 ivacaftor 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, the statements submitted in the written statement and oral hearing procedure. 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 ivacaftor.

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

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

2.1.1 Approved therapeutic indication of Ivacaftor (Kalydeco) in accordance with the product information

Kalydeco tablets are indicated in a combination regimen with ivacaftor/ tezacaftor/ elexacaftor tablets for the treatment of adults, adolescents and children aged 6 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene.

Therapeutic indication of the resolution (resolution of 4 August 2022):

Kalydeco tablets are indicated in a combination regimen with ivacaftor/ tezacaftor/ elexacaftor tablets for the treatment of cystic fibrosis in patients aged 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children aged 6 to 11 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele

Appropriate comparator therapy for Ivacaftor in combination with Ivacaftor/ Tezacaftor/ Elexacaftor:

Ivacaftor

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. The following medicinal products are approved for the treatment of CF:

The CTFR modulator ivacaftor is approved for the patient group to be considered in the present therapeutic indication "children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele".

Furthermore, the following medicinal products are approved for the symptomatic therapy of CF: aztreonam, carbocisteine[2], ceftazidime, ciprofloxacin, colistimethate, dornase alfa, Meronem, pancreatin, tobramycin.

on 2. In the treatment of CF, nutritional measures, support of the respiratory function and physiotherapy (in the sense of the Remedies Directive) are basically considered as non-medicinal treatment.

on 3. There are no resolutions of the G-BA for the patient group to be considered in the present therapeutic indication "children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele".

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

The above medicinal and non-medicinal treatment options are available for children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (incl. R117H) on the second allele. The active ingredient ivacaftor is approved in the present therapeutic indication and is therefore determined as the appropriate comparator therapy.

Patients should also be offered symptomatic therapy, if indicated, with the above medicinal and non-medicinal treatment options. These are recommended in the present evidence for symptomatic therapy of CF, especially antibiotic therapy of pulmonary infections (ceftazidime, colistimethate, tobramycin), inhaled medicinal products (dornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin) and nutritional therapy

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor is assessed as follows:

<u>Children aged 6 to 11 years with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele</u>

An additional benefit is not proven.

[2] Currently off the market

Justification:

The pharmaceutical company did not submit any direct comparator studies versus the appropriate comparator therapy for the assessment of the additional benefit of ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor in children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele.

A transfer of the additional benefit on the basis of the information provided by the pharmaceutical company is neither possible from patients with a deviating mutation type nor from older patients to the population in the present therapeutic indication.

For the transfer of the additional benefit between different mutation types, the pharmaceutical company argues purely qualitatively about the mode of action of the intervention and does not present any data on patient-relevant endpoints for the patients relevant in the present research question. In addition, the pharmaceutical company's argumentation for the transfer of additional benefit between different mutation types is based, among other things, on the results of the RCT VX19-445-116 study, for which a deviating appropriate comparator therapy was determined.

The significant VX18-445-104 study, which the pharmaceutical company uses for its argumentation for the transfer of the additional benefit of patients aged 12 years and older, was already assessed as being unsuitable in the context of the benefit assessments for this age group due to a too short study duration, and the additional benefit was assessed as not proven for this age group.

An additional benefit of ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor compared with the appropriate comparator therapy is therefore not proven in the present therapeutic indication.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor. Ivacaftor (invented name: Kalydeco) was approved as an orphan drug but has exceeded the EUR 50 million turnover limit.

The present resolution refers to the therapeutic indication "Kalydeco tablets are indicated in a combination regimen with ivacaftor/ tezacaftor/ elexacaftor tablets for the treatment of cystic fibrosis in patients aged 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele."

The G-BA determined ivacaftor as appropriate comparator therapy.

For the benefit assessment of ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor, no direct comparator studies versus the appropriate comparator therapy were presented in the present therapeutic indication.

A transfer of the additional benefit on the basis of the information provided by the pharmaceutical company is neither possible from patients with a deviating mutation type nor from older patients to the population in the present therapeutic indication.

Therefore, the overall assessment does not demonstrate any additional benefit for children aged 6 to 11 years with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including R117H) on the second allele.

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

In order to ensure consistent consideration of the patient numbers taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication of cystic fibrosis, the G-BA uses the following derivation of the patient numbers:

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

Altogether, it is assumed that there are currently about 8,000 patients with cystic fibrosis in Germany[3].

This amount differs from the calculation of the pharmaceutical company in the dossier, which assumes 6,648 patients with cystic fibrosis in the total population. However, this figure is subject to uncertainties and is underestimated, as those patients without process data and without a current informed consent form were not taken into account here. In addition, there is currently no evidence that the overall patient population has changed meaningfully since the 2012 reporting volume (8,042 patients ever reported and alive at the time. This figure has already been adjusted for multiple responses according to the information in the report volume).

Therefore, the number of 28 patients in the SHI target population calculated by the pharmaceutical company especially represents an underestimation in the overall assessment.

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 Kalydeco (active ingredient: ivacaftor) at the following publicly accessible link (last access: 13 July 2022):

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

Treatment with ivacaftor should only be initiated and monitored by doctors experienced in the therapy of children with cystic fibrosis.

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 2022).

[3] Mukoviszidose e.V. - Federal Association for Cystic Fibrosis (CF) Website Mukoviszidose e.V.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation only the dosages of the general case are considered. If the treatment duration is not limited, initial induction schemes are not considered for the cost representation. Patient-individual dose adjustments (e.g., because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

For dosage depending on body weight, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied. The average body weight of 6-year-olds is 23.6 kg and that of 11-year-olds 42.1 kg. The dosage of ivacaftor/ tezacaftor/ elexacaftor recommended for children varies depending on body weight. According to the product information, children up to a body weight of 30 kg receive 1 x daily 2 tablets of 37.5 mg/ 25 mg/50 mg ivacaftor/ tezacaftor/ elexacaftor and 1 x daily 1 tablet of 75 mg ivacaftor. Above a body weight of 30 kg, children receive 1 x daily 2 tablets of 75 mg/ 50 mg/ 100 mg ivacaftor/ tezacaftor/ elexacaftor and 1 x daily 1 tablet of 150 mg ivacaftor.

For ivacaftor monotherapy, children with less than 25 kg body weight receive 75 mg ivacaftor granules 2 x daily. Children with a body weight of 25 kg or more receive monotherapy with ivacaftor 150 mg 2 x daily in the form of film-coated tablets.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ivacaftor	continuously, 1 x daily	365	1	365
Ivacaftor/ tezacaftor/ elexacaftor	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Ivacaftor	continuously, 2 x daily	365	1	365

Consumption:

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					
Ivacaftor	75 mg - 150 mg	75 mg - 150 mg	1 x 75 mg - 1 x 150 mg	365	365 x 75 mg - 365 x 150 mg
Ivacaftor/ tezacaftor/ elexacaftor	75 mg/ 50 mg/ 100 mg - 150 mg/ 100 mg/ 200 mg	75 mg/ 50 mg/ 100 mg - 150 mg/ 100 mg/ 200 mg	2 x 37.5 mg/ 25 mg/ 50 mg - 2 x 75 mg/ 50 mg/ 100 mg	365	730 x 37.5 mg/ 25 mg/ 50 mg - 730 x 75 mg/ 50 mg/ 100 mg
Appropriate comparator therapy					
Ivacaftor	75 mg - 150 mg	150 mg - 300 mg	2 x 75 mg - 2 x 150 mg	365	730 x 75 mg - 730 x 150 mg

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.

Costs of the medicinal products:

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					
Ivacaftor 75 mg	28 FCT[4]	€ 6,751.63	€ 1.77	€ 384.99	€ 6,364.87
Ivacaftor 75 mg	56 GRA[5]	€ 13,492.83	€ 1.77	€ 769.98	€ 12,721.08
Ivacaftor 150 mg	56 FCT[4]	€ 13,492.83	€ 1.77	€ 769.98	€ 12,721.08

[4] According to the product information, approved as monotherapy only for children with a body weight of 25 kg or more.

[5] According to the product information, approved for children with a body weight between 5 kg and less than 25 kg.

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
Ivacaftor 37.5 mg/ tezacaftor 25 mg/ elexacaftor 50 mg	56 FCT	€ 12,738.95	€ 1.77	€ 726.93	€ 12,010.25
Ivacaftor 75 mg/ tezacaftor 50 mg/ elexacaftor 100 mg	56 FCT	€ 12,738.95	€ 1.77	€ 726.93	€ 12,010.25
Appropriate comparator therapy					
Ivacaftor 75 mg	56 GRA[5]	€ 13,492.83	€ 1.77	€ 769.98	€ 12,721.08
Ivacaftor 150 mg	56 FCT[4]	€ 13,492.83	€ 1.77	€ 769.98	€ 12,721.08
Abbreviations: FCT = film-coated tablets, GRA = granules					

LAUER-TAXE® last revised: 15 July 2022

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 had to be taken into account.

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 11 January 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 3 February 2022, the pharmaceutical company submitted a dossier for the benefit assessment of ivacaftor to the G-BA in due time in accordance with Chapter 5, Section 8,

paragraph 1, number 1, sentence 2 VerfO [depending on the procedure, add: number 2, 3, 4, 5, 6, 7 and 8].

By letter dated 9 February 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 ivacaftor.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 May 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 16 May 2022. The deadline for submitting written statements was 7 June 2022.

The oral hearing was held on 27 June 2022.

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 26 July 2022, and the proposed resolution was approved.

At its session on 4 August 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 January 2021	Determination of the appropriate comparator therapy
Working group Section 35a	21 June 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 June 2022	Conduct of the oral hearing
Working group Section 35a	6 July 2022 20 July 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	26 July 2022	Concluding discussion of the draft resolution
Plenum	4 August 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 August 2022

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

Prof. Hecken