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 with ivacaftor/ tezacaftor/ elexacaftor in subjects aged 12 years and older (heterozygous for F508del and gating mutation (including R117H))

of 19 November 2021

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 studies 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 benefits,
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 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 forms 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.

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. Proof 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 26 April 2021, 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 20 May 2021, 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 ("treatment of cystic fibrosis in patients aged 12 years or older who are heterozygous for the F508del mutation in the CFTR gene and carry a gating mutation (including the R117H 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 1 September 2021, 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 and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene.

Therapeutic indication of the resolution (resolution from 19 November 2021):

Kalydeco tablets are indicated in a combination regimen with ivacaftor/ tezacaftor/ elexacaftor tablets for the treatment of cystic fibrosis in subjects aged 12 years and older 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 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Subjects aged 12 years and older 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 Federal Joint Committee has already determined the patient-relevant benefit 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 active ingredient ivacaftor is approved for the patient group to be considered in the present therapeutic indication "subjects aged 12 years and older 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".

The following medicinal products are approved for the symptomatic therapy of CF:

aztreonam, carbocisteine[2], ceftazidime, ciprofloxacin, colistimethate, dornase alfa, levofloxacin[3], Meronem, mannitol, 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.

[2] currently off the market
[3] Only approved for adult patients with CF

on 3. There are no resolutions for the patient group to be considered in the present therapeutic indication "subjects aged 12 years and older 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 accepted state of medical knowledge was established using a search for guidelines and systematic reviews of clinical studies. The above medicinal and non-medicinal treatment options are available for symptomatic therapy of subjects aged 12 years and older with cystic fibrosis, who are heterozygous for the F508del mutation in the CFTR gene and have a gating mutation (including R117H) on the second allele. In the present evidence, medicinal therapy with ivacaftor is recommended. Therefore, ivacaftor is determined to be the appropriate comparator therapy in the present indication.

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 (mannitol, dornase alfa), enzyme substitution for pancreatic insufficiency (pancreatin), nutritional therapy and support of respiratory function and physiotherapy.

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>Subjects aged 12 years and older 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.

Justification:

The pharmaceutical company submitted the multicentre, randomised, double-blind, controlled phase III study VX18-445-104 (hereinafter study 104), justifying the marketing authorisation, for the evaluation of the additional benefit of ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor in subjects aged 12 years and older 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.

This study included patients aged 12 years and older with cystic fibrosis who had a heterozygous F508del mutation in the CFTR gene. The second allele had to have either a gating mutation (including the R117H mutation) or an RF mutation. Furthermore, patients had to show a forced expiratory volume in one second (FEV_1) between ≥ 40% and ≤ 90% of the standardised normal value for age, sex and height at the time of screening.

In the intervention arm, treatment was with ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor. For the control, different comparator therapies were offered, depending on the type of mutation present on the second allele. Relevant to the present assessment is the sub-population with a gating mutation (including the R117H mutation) and, accordingly, the comparator arm in which treatment with ivacaftor alone was offered. The relevant sub-population includes 50 and 45 participants in the intervention and comparator arm, respectively. According to the study protocol, the respective pretreatment of the patients was to be continued at a stable dose, but individual adjustments were made in some cases.

The primary endpoint of study 104 was the "absolute change in FEV1%" (percentage of forced expiratory volume in one second) compared to the start of the study. In addition, endpoints in the categories of mortality, morbidity, quality of life and side effects were collected.

The study consisted of a 28-day run-in phase, followed by an 8-week treatment phase and a 28-day follow-up phase. Following the treatment phase, there was an opportunity to participate in an open-label extension study.

The 8-week treatment phase chosen by the pharmaceutical company was considered sufficient for marketing authorisation to demonstrate the efficacy or efficacy profile of ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor in the presence of a heterozygous F508del mutation and a gating mutation on the second allele.

However, this study duration is too short for the assessment of effects on patient-relevant endpoints of a medicinal product to be able to make a valid assessment of the additional benefit in chronic disease.

Cystic fibrosis is a chronic, progressive disease with no remedy option and requiring lifelong treatment. The European Medicines Agency (EMA) guideline[4] specifies a minimum duration of 6 months for the investigation of a clinical endpoint in the present therapeutic indication.

A treatment phase of only 8 weeks does not take into account the patient-individual fluctuations in clinical symptomatology, which can be modified by various factors. Furthermore, on the basis of short-term studies, no conclusions can be drawn as to whether short-term effects persist in the longer term. It is also not possible to record effects that only become apparent in the longer term, such as for pulmonary exacerbations and their consequences or for adverse events (AEs). Pulmonary exacerbations are a common cause of lung injury or death in patients with cystic fibrosis.

In the therapeutic indication of cystic fibrosis, short-term studies (with a treatment duration of less than 24 weeks) are unsuitable for the benefit assessment. Against this background, study 104 cannot be used for the benefit assessment.

For the present relevant patient population, the pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor compared with the appropriate comparator therapy.

[4] European Medicines Agency. Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis [online]. 22.10.2009 [accessed on: 22.10.2021]. URL: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-development-medicinal-products-treatment-cystic-fibrosis-first-version_en.pdf.

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.

This resolution refers to the therapeutic indication "as part of a combination regimen with ivacaftor/ tezacaftor/ elexacaftor tablets for the treatment of cystic fibrosis in subjects aged 12 years and older, 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.

The 8-week, multicentre, randomised, double-blind, controlled phase III study VX18-445-104 was submitted for the benefit assessment of ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor for the present therapeutic indication.

This 8-week study is too short for the benefit assessment. For this patient population, the pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of ivacaftor in combination with ivacaftor/ tezacaftor/ elexacaftor compared with the appropriate comparator therapy.

Therefore, the overall assessment does not demonstrate any additional benefit for subjects aged 12 years and older, 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 resolution (18 February 2021) 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[5].

This amount differs from the calculation of the pharmaceutical company in the dossier, which assumes 6,340 patients with cystic fibrosis in the total population. However, this figure is subject to uncertainties and is underestimated, as those patients without follow-up 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 133 patients in the SHI target population calculated by the pharmaceutical company especially represents an underestimation in the overall assessment.

[5] Mukoviszidose e.V. - Federal Association for Cystic Fibrosis (CF) Website Mukoviszidose e.V. [accessed on 27.06.2019]

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: 11 October 2021):

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 treating adolescents and adult patients 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: 1 November 2021).

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

Treatment period:

The treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient 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.

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

Costs:

In order to improve comparability, the costs of the medicinal products were recorded approximately as well as on the basis of rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on 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 150 mg	56 FCT	€ 13,492.59	€ 1.77	€ 769.98	€ 12,720.84
Elexacaftor/ tezacaftor/ ivacaftor 75 mg/50 mg/100 mg	56 FCT	€ 12,867.29	€ 1.77	€ 734.27	€ 12,131.25
Appropriate comparator therapy					
Ivacaftor 150 mg	56 FCT	€ 13,492.59	€ 1.77	€ 769.98	€ 12,720.84

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 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 25 February 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. At its session on 27 April 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 20 May 2021, 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 2 VerfO.

By letter dated 27 May 2021, 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 30 August 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 September 2021. The deadline for submitting written statements was 22 September 2021.

The oral hearing was held on 11 October 2021.

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 9 November 2021, and the proposed resolution was approved.

At its session on 19 November 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	25 February 2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	27 April 2021	New determination of the appropriate comparator therapy
Working group Section 35a	5 October 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	11 October 2021	Conduct of the oral hearing,
Working group Section 35a	19 October 2021 2 November 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	9 November 2021	Concluding discussion of the draft resolution
Plenum	19 November 2021	Adoption of the resolution on the amendment of Annex XII AM-RL (Pharmaceuticals Directive)

Berlin, 19 November 2021

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

Prof. Hecken