Gemeinsamer Bundesausschuss

Justification

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII - Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredient according to Section 35a SGB V Ivacaftor (new therapeutic indication: cystic fibrosis, patients from 4 < 6 months, R117H-Mutation)

of 20 May 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 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

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marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th 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.

Within the previously approved therapeutic indications, the sales volume of ivacaftor with the statutory health insurance at pharmacy retail prices 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 3 November 2020, 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 2a letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 24 November 2020, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company on the approval of a new area of application, the pharmaceutical company has submitted a dossier 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, patients from 4 < 6 months, R117H-Mutation).

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 March 2021 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of 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, and the addenda to the benefit assessment prepared by the IQWiG. 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 granules are used to treat infants 4 months of age and older, toddlers and children weighing between 5 kg and less than 25 kg with cystic fibrosis (CF, mucoviscidosis) who have an R117H CFTR-Mutation or one of the following gating mutations (class III) in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

Therapeutic indication of the resolution (resolution from the 20/5/2021):

Kalydeco granules are used to treat infants with cystic fibrosis aged 4 < 6 months who have an R117H-Mutation in the CFTR gene

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Infants with cystic fibrosis aged 4 to < 6 months who have an R117H-Mutation in the CFTR gene

Appropriate comparator therapy for ivacaftor:

- Best supportive care

Best Supportive Care (BSC) is understood to be the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve the quality of life (in particular antibiotics for pulmonary infections, mucolytics, pancreatic enzymes for pancreatic

1 General Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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insufficiency, physiotherapy (as defined in the Remedies Directive), with exhaustion of all possible dietary measures).

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 Federal Joint Committee 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:

zu 1. The following medicinal products are approved for the symptomatic therapy of CF: aztreonam[2], carbocisteine[3], ceftazidime, ciprofloxacin, colistimethate, dornase alfa, levofloxacin[4], meronem, mannitol[4], pancreatin, tobramycin[2].

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-drug treatment.

on 3. For the patient group to be considered in the indication "infants with cystic fibrosis aged 4 to < 6 months who have an R117H-Mutation in the CFTR gene" no resolutions are available.

The following resolutions of the G-BA on the early benefit assessment in elderly patients with cystic fibrosis who have an R117H-Mutation in the CFTR gene:

- Ivacaftor, resolution of 17 December 2020, patients aged 6 months < 18 years, indication of a non-quantifiable additional benefit
- Ivacaftor, resolution of 20 February 2020, patients 18 years of age and older, evidence of minor additional benefit

on 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines and systematic reviews of clinical studies. For patients with cystic fibrosis aged 4 < 6 months, there is no specific standard therapy

2 approved from 6 years
3 currently not available
4 only approved for adults

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according to the current state of medical knowledge. The above-mentioned medicinal and non-drug therapy options are available for symptomatic therapy. These are recommended in the present evidence for symptomatic therapy of CF, especially antibiotic therapy of pulmonary infections (ceftazidine, colistimethate, tobramycin), inhalation of drugs (mannitol, dornase alfa), enzyme substitution in pancreatic insufficiency (pancreatin), nutritional therapy and support of respiratory function, physiotherapy. In CF, treatment is thus patient-individual in order to alleviate symptoms and improve quality of life in the sense of Best Supportive Care (BSC).

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ivacaftor is assessed as follows:

Infants with cystic fibrosis aged 4 to < 6 months who have an R117H-Mutation in the CFTR gene

Hint of non-quantifiable additional benefit

Justification: *[Note GS: see D-555 PatPop a) Ivacaftor R117H from 6 months < 6 years]*

Extensive data are not available for the benefit assessment of ivacaftor in infants with cystic fibrosis aged 4 < 6 months who have an R117H-Mutation in the CFTR gene. In the single-arm, open-label, phase III, pivotal VX15-770-124 study, the appropriately relevant patient population included 7, a total of 6 infants 4 < 6 months of age[5]. Among them was one infant with R117H-Mutation, but no separate presentation of the corresponding data was made. The pharmaceutical company therefore transfers the results of ivacaftor treatment in adults with the same mutation to patients aged 4 < 6 months.

The European Medicines Agency extrapolated adult data to demonstrate efficacy and extrapolated data from children with gating mutations to demonstrate safety in infants with cystic fibrosis aged 4 <6 months with an R117H-Mutation as part of the approval of ivacaftor.

The findings of the European Medicines Agency (EMA)[6] on the medical rationale for transferring data from older patient groups or patients with other mutations to infants with cystic fibrosis aged 4 < 6 months with R117H-Mutation are also decisive for the G-BA in deriving the additional benefit in the present benefit assessment.

Cystic fibrosis is an inherited multisystem disease in which mutations in the CFTR gene cause disruptions in the chloride channel of exocrine glands. Thus, the pathophysiological background (disruption in the chloride channel) is identical for the patient group of 4 months

[5]CF patients with gating mutations (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R): 4 < 6 months with resolution dated 20 May 2021 https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/616/ *[accessed 6 May 2021]*

[6]Assessment Report; EMEA/H/C/002494/II/0086 dated 17 September 2020; Available from: https://www.ema.europa.eu/en/documents/variation-report/kalydeco-h-c-2494-ii-0086-epar-assessment-report-variation_en.pdf [Accessed 22 April 2021]

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< 6 months old infants and the older patients. Treatment with ivacaftor modulates the functionality of the chloride channels regardless of the age of the patient.

The course of cystic fibrosis is progressive, i.e. the manifestation becomes stronger with increasing age, so that younger patients with cystic fibrosis still show relatively few symptoms. Accordingly, patients aged 6 years- < 18 years with the same mutation in the CFTR gene, showed only a low symptom burden in the VX11-770-110 study. Therefore, it cannot be assumed that the effects of treatment could be reproduced in this even younger age group.

In adult patients with cystic fibrosis and an R117H-Mutation, an indication for a minor additional benefit was already derived in a resolution dated 20 February 2020. In study 110, ivacaftor showed an advantage over the appropriate comparator therapy BSC both in the symptomatology of the respiratory system and in the quality-of-life endpoints of emotional state and vitality of the CFQ-R (for further information, please refer to the justification of the resolution).

The appropriate comparator therapy defined by the G-BA for infants aged 4 < 6 months and for patients aged 18 years and older with an R117H-Mutation in the CFTR gene[7] as well as for patients with certain gating mutations[8] is identical (Best Supportive Care), thus fulfilling a criterion for evidence transfer in the benefit assessment. The standards to be applied for the acceptance of evidence from other patient groups will also take into account the specificities and limitations in the conduct of paediatric clinical trials.

With regard to the safety profile, according to the EMA's comments in the assessment report[5] on ivacaftor, it cannot be assumed that there are differences between the various mutations. In the present benefit assessment, the results of patients from 4 < 6 months with gating mutations were also taken into account. Insgesamt konnte im Rahmen der Nutzenbewertungen bezüglich der Sicherheit kein Nachteil von Ivacaftor + BSC gegenüber Placebo + BSC festgestellt werden.

Given the presence of an identical underlying genetic cause of the disease and thus a comparable pathophysiology, the additional benefit identified is assumed to be transferable from the population of ≥ 18-year-old patients with an R117H-Mutation to the population of 4-month- < 6-month-old infants with the same mutation. Due to the associated uncertainties and limitations of the available evidence, the magnitude of the additional benefit is not quantifiable.

Overall assessment/conclusion

Overall, the G-BA concludes that the transferability of the additional benefit to ivacaftor from patients aged 18 years and older to infants with cystic fibrosis aged 4 < 6 months who have an R117H-Mutation in the CFTR gene is assumed, particularly against the background of the comparable disease picture, the progressive course and the limitations in conducting clinical trials in this age group, taking into account the data on the safety of children with gating mutations.

However, the additional benefit is not quantifiable, as the scientific data situation does not allow this at the present time.

[7]CF patients with R117H-Mutation 18 years of age and older with resolution dated 20 February 2020
[8]CF patients with gating mutations (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R): 6-<12 months with resolution of 4 June 2020; 12 - < 24 months with resolution of 20 February 2020; 2 - 5 years with resolution of 20 February

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Reliability of data (probability of additional benefit)

Due to the uncertainty caused by the transfer of the additional benefit to a younger population, an overall indication is derived.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient ivacaftor. Kalydeco® was approved as an orphan drug, but has exceeded the EUR 50 million turnover limit.

The present resolution refers to the indication "Infants with cystic fibrosis aged 4 to < 6 months who have an R117H-Mutation in the CFTR gene".

The appropriate comparator therapy of Best Supportive Care was determined as follows by the G-BA.

The pharmaceutical company does not present comparative studies and transfers the results of ivacaftor treatment in adults with R117H-Mutation to patients aged 4 < 6 months.

In particular, against the background of the comparable disease pattern, the progressive course and the limitations in the conduct of clinical trials, the G-BA concludes that the transferability of the additional benefit from adults (resolution of 20 February 2020) to infants aged 4 < 6 months with cystic fibrosis and an R117H-Mutation in this age group is assumed, taking into account the data on the safety of children with gating mutations.

Due to the uncertainty caused by the transfer of the additional benefit to a younger population, a hint of non-quantifiable additional benefit can be identified.

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

In order to ensure a consistent consideration of the patient numbers taking into account the most recent resolution (18 February 2021) on the benefit assessment of drugs with new active ingredients according to Section 35a SGB V in the therapeutic area 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[9].

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).

The number of 1 patient in the SHI target population calculated by the pharmaceutical company is consistent with IQWIG's own calculations. However, it should be noted that using

[9]https://www.muko.info/ Mukoviszidose e.V. Website [accessed 27.6.2019].

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the proportion values for the mutations determined by the pharmaceutical entrepreneur, there are mathematically 0 patients who have an R117H-Mutation in the CFTR gene.

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: 6 May 2021):
https://www.ema.europa.eu/documents/product-information/kalydeco-epar-product-information_de.pdf

Treatment with ivacaftor should only be initiated and monitored by doctors experienced in treating 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 May 2021).

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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular strength was first determined on the basis of consumption. Having determined the number of packs of a particular strength, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

For the calculation of the dosages, the dosage recommendations of the expert information are decisive. Accordingly, infants aged 4 months < 6 months are assumed to have a bodyweight of at least 5 kg (≥ 5 kg < 7 kg). In this patient, a single dose of 25 mg ivacaftor granules every 12 hours is recommended, resulting in a total daily dose of 50 mg.

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.

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.

Patients in the present application area receive the best supportive care. The treatment costs for best supportive care are different for each individual patient.

Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed.

The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

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Treatment duration:

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ year
Medicinal product to be assessed				
Ivacaftor	continuously, twice daily	365	1	365
Best supportive care	Patient-individual			
Appropriate comparator therapy				
Best supportive care	Patient-individual			

Consumption:

Name of therapy	Dosage/ application	Dosage/ patient/ days of treatmen t	Usage by strength/day of treatment	Days of treatmen t/ patient/ year	Average annual consumption by strength
Medicinal product to be assessed					
Ivacaftor	25 mg	50 mg	twice 25 mg	365	730 x 25 mg
Best supportive care	Patient-individual				
Appropriate comparator therapy					
Best supportive care	Patient-individual				

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Costs:

Costs of the medicinal product:

Name of 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 50 mg	56 GRA	€16,432.12	€ 1.77	€ 937.86	€ 15,492.49
Best supportive care	Patient-individual				
Appropriate comparator therapy					
Best supportive care	Patient-individual				
Abbreviations: GRA = Granules in a bag					

LAUER-TAXE® last revised: 1 May 2021

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 cost 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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 10 November 2020.

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On 24 November 2020, 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.

By letter dated 26 November 2020 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 25 February 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2021. The deadline for submitting written statement procedures was 22 March 2021.

The oral hearing was held on 6 April 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 were discussed at the session of the subcommittee on 11 May 2021, and the draft resolution was approved.

At its session on 20 May 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 November 2020	Determination of the appropriate comparator therapy
Working group Section 35a	31 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	6 April 2021	Conduct of the oral hearing
Working group Section 35a	14 April 2021 5 May 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	11 May 2021	Concluding consultation of the draft resolution
Plenum	20 May 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 May 2021

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Federal Joint Committee in accordance with Section 91 SGB V The chairman

Prof. Hecken

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