Justification

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):
Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Tezacaftor/Ivacaftor (new therapeutic indication: cystic fibrosis, combination therapy with Ivacaftor in patients aged 6 < 12 years (homozygous or F508del-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 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:

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 combination of active ingredients tezacaftor/ivacaftor (Symkevi) was listed for the first time on 1 December 2018 in the "LAUER-TAXE®", the extensive German registry of available medicinal products and their prices.

Within the previously approved therapeutic indications, the sales volume of tezacaftor/ivacaftor with the statutory health insurance at pharmacy sales prices including value-added tax exceeded € 50 million. Proof must therefore be provided for tezacaftor/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 25 November 2020, Vertex Pharmaceuticals GmbH 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 30 November 2020, 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 combination of active ingredients tezacaftor/ivacaftor with the new therapeutic indication (cystic fibrosis, combination therapy with ivacaftor in patients aged 6 < 12 years (homozygous or F508del-Mutation).

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 at (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 tezacaftor/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, and 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 tezacaftor/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 tezacaftor/ivacaftor (Symkevi) in accordance with the product information

Symkevi is used as a combination treatment with ivacaftor tablets for the treatment of cystic fibrosis (CF) in patients 6 years of age and older who are homozygous for the F508del-Mutation or heterozygous for the F508del-Mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR gene): P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

Therapeutic indication of the resolution (resolution of 20 May 2021):

Symkevi is used as a combination treatment with ivacaftor tablets for the treatment of cystic fibrosis (CF) in children 6 years < 12 years of age who are homozygous for the F508del-Mutation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children with cystic fibrosis aged 6 < 12 years who are homozygous for the F508del-Mutation.

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

Lumacaftor/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 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:

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

For the patient group to be considered in the present indication “patients from 6 < 12 years of age with cystic fibrosis who are homozygous for the F508del-Mutation”, the active ingredient combination lumacaftor/ivacaftor (LUM/IVA; CFTR modulators) is approved.

For the symptomatic treatment of CF, the following medicinal products are also approved: aztreonam[2], carbocisteine[3], ceftazidime, ciprofloxacin, colistimethate, dornase alfa[2], levofloxacin[4], meronem, mannitol[4], pancreatin, tobramycin.

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

on 3. For the patient group to be considered in the present indication “patients from 6 < 12 years of age with cystic fibrosis who are homozygous for the F508del-Mutation”, the following decisions of the G-BA are available:

- For LUM/IVA, there is a hint of non-quantifiable additional benefit for the patient group “children aged 6 years to 11 years inclusive” (resolution of 2 August 2018).

[2] approved for ages 6 and up
[3] currently off the market
[4] approved for adults only

For patients who are homozygous for the F508del-Mutation in the CFTR gene, the G-BA has passed the following further resolutions on an amendment to the AM-RL: Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- For LUM/IVA, a non-quantifiable additional benefit was identified for the patient group "children aged 2 years to 5 years inclusive" (decision of 15 August 2019).
- For LUM/IVA, an indication of substantial additional benefit was identified for the patient group "patients aged 12 years and older" (decision of 2 June 2016).
- No additional benefit was identified for ivacaftor (resolution of 20 February 2020) as a combination treatment with tezacaftor/ivacaftor (resolution of 17 December 2020) for the patient group "patients aged 12 years and over".
- For ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor, an indication of significant additional benefit was identified for the patient group "patients aged 12 years and older" (decision of 18 February 2021).

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 CF aged 6 years and older who are homozygous for the F508del-Mutation in the CFTR gene, the above drug and non-drug treatment options are available. In the present evidence, medicinal product therapy with LUM/IVA is recommended. In the present indication, LUM/IVA is therefore determined to be 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 (ceftazidine, colistimethate, tobramycin), inhaled drugs (mannitol, dornase alfa), enzyme substitution in 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 order.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of tezacaftor/ivacaftor in combination with ivacaftor (TEZ/IVA + IVA) is assessed as follows:

For children with cystic fibrosis aged 6 < 12 years who are homozygous for the F508del-Mutation, the additional benefit of tezacaftor/ivacaftor in combination with ivacaftor compared with the appropriate comparator therapy is not proven.

Purpose:

In the assessment of the additional benefit of TEZ/IVA + IVA, the pharmaceutical company does not present any direct comparative studies compared to the appropriate comparator therapy LUM/IVA. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment.

For the demonstration of the additional benefit of TEZ/IVA + IVA in children aged 6 < 12 years with cystic fibrosis who are homozygous with respect to the F508del-Mutation, the single-arm study VX13-661-113 (hereafter Study 113) was submitted by the pharmaceutical company. Study 113 consisted of two parts, the first being a 14-day treatment and the second a 24-week treatment with TEZ/IVA + IVA. Only the second part is referred to in the pharmaceutical company's dossier. A total of 70 children with cystic fibrosis were included in the second part of the study. Of these, 61 children (87%) are homozygous, and 9 children (12.9%) are heterozygous for the F508del-Mutation.

The dosing with TEZ/IVA + IVA in study 113 deviated from the requirements of the product information for about one third of the children. Because children received the higher dosage of the intervention only at a bodyweight ≥ 40 kg instead of at a bodyweight ≥ 30 kg according to the product information, children with a bodyweight ≥ 30 kg < 40 kg were underdosed.

The single-arm study 113 is not relevant for the present benefit assessment because no data are available for an assessment of TEZ/IVA + IVA compared with the appropriate comparator therapy.

In addition, the results of the 8-week RCT VX16-661-115 (TEZ/IVA + IVA vs placebo; hereinafter Study 115) and the single-arm extension study VX17-661-116 (hereinafter Study 116) were presented by the pharmaceutical company. The pharmaceutical company does not use both studies to derive the additional benefit. In the therapeutic area of cystic fibrosis, short-term studies (with a treatment duration of less than 24 weeks) are not suitable for the benefit assessment. Study 115 cannot be used for the benefit assessment because the study duration is too short, and the appropriate comparator therapy has not been implemented. In study 116, no comparison was made with the appropriate comparator therapy; consequently, it is also not considered for the present 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 TEZ/IVA + IVA compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication of the combination of tezacaftor/ivacaftor in combination with ivacaftor (TEZ/IVA + IVA). This assessment is for the indication "for the treatment of cystic fibrosis (CF) in children aged 6 years < 12 years who are homozygous for the F508del-Mutation."

Tezacaftor/Ivacaftor has an orphan drug designation but has exceeded the EUR 50 million turnover limit.

The G-BA lumacaftor/ivacaftor determined the appropriate comparator therapy.

For the assessment of the additional benefit of TEZ/IVA + IVA, the single-arm study VX13-661-113 (24 weeks) was submitted by the pharmaceutical company. Study 113 is not relevant for the present benefit assessment because no data are available on the appropriate comparator therapy.

Supplementary results from the 8-week RCT VX16-661-115 (TEZ/IVA + IVA vs placebo) and the single-arm extension study VX17-661-116 were listed. In studies 115 and 116, no comparison

was made with the appropriate comparator therapy, and study 115 had a too short study duration, which is why they are also not considered for the present benefit assessment.

For this patient population no study was presented that would have been suitable for the assessment of the additional benefit of TEZ/IVA + IVA compared with the appropriate comparator therapy.

Overall, for patients aged 6 years < 12 years with cystic fibrosis who are homozygous for the F508del-Mutation in the CFTR gene, an additional benefit is therefore not proven.

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

Children with cystic fibrosis aged 6 < 12 years who are homozygous for the F508del-Mutation

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 8000 patients with cystic fibrosis in Germany[5].

This amount differs from the calculation of the pharmaceutical company in the dossier, which assumes 6340 patients with cystic fibrosis in the total collective. 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 (8042 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).

1. The percentage of patients with confirmed homozygous F508del mutation in the CFTR gene is 46.4%[6] (3712 patients).
2. The proportion of patients aged 6 < 12 years in the total collective is approximately 14.2%3 (527 patients).
3. Taking into account a proportion of 87.89% of patients insured by the SHI, there are 467 patients in the target population.

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

[5] https://www.muko.info/ Mukoviszidose e.V. website. [Accessed 27 Jun. 2019].

[6] Nährlich L, Burkhart M, Wosniok J. German Mucoviscidosis Registry: Report Volume 2018. 2019 https://www.muko.info/fileadmin/user_upload/angebote/qualitaetsmanagement/register/berichtsbaende/berichtsband_2018.pdf.

product characteristics, SmPC) for Symkevi (active ingredient: tezacaftor/ivacaftor) at the following publicly accessible link (last access: 1 April 2021):
https://www.ema.europa.eu/en/documents/product-information/symkevi-epar-product-information_de.pdf

Treatment with tezacaftor/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).

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

Treatment duration:
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.

Name of therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Tezacaftor/Ivacaftor	continuously, once daily	365	1	365
Ivacaftor	continuously, once daily	365	1	365
Appropriate comparator therapy				
Lumacaftor/Ivacaftor	Continuously, 2 x every 12 days	365	1	365

Consumption:

Name of therapy	Dosage/application	Dosage/patient/days of treatment	Usage by strength/ day of treatment	Days of treatment/ patient/ year	Average annual consumption by strength
Medicinal product to be assessed					

Name of therapy	Dosage/application	Dosage/patient/days of treatment	Usage by strength/ day of treatment	Days of treatment/ patient/ year	Average annual consumption by strength
Children from 6 - 8 years (< 30 kg):					
Tezacaftor/Ivacaftor	50 mg/75 mg	50 mg/75 mg	1 x 50 mg/75 mg	365	365 x 50 mg/75 mg
Ivacaftor	75 mg	75 mg	1 x 75 mg	365	365 x 75 mg
Children from 9 - 11 years (≥ 30 kg):					
Tezacaftor/Ivacaftor	100 mg/150 mg	100 mg/150 mg	1 x 100 mg/150 mg	365	365 x 100 mg/150 mg
Ivacaftor	150 mg	150 mg	1 x 150 mg	365	365 x 150 mg
Appropriate comparator therapy					
Lumacaftor/Ivacaftor	200 mg/250 mg	400 mg/500 mg	4 x 100 mg/125 mg	365	1460 x 100 mg/125 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 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.

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					
Tezacaftor/ivacaftor 50 mg/75 mg	28 FCT	€ 5,292.22	€ 1.77	€ 301.66	€ 4,988.79
Tezacaftor/ivacaftor 100 mg/150 mg	28 FCT	€ 5,292.22	€ 1.77	€ 301.66	€ 4,988.79
Ivacaftor 75 mg	28 FCT	€ 8,221.15	€ 1.77	€ 468.93	€ 7,750.45
Ivacaftor 150 mg	56 FCT	€ 16,432.12	€ 1.77	€ 937.86	€ 15,492.49
Appropriate comparator therapy					

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
Lumacaftor/ivacaftor 100 mg/125 mg	112 FCT	€ 12,076.19	€ 1.77	€ 689.09	€ 11,385.33
Abbreviations: FCT = Film-coated tablets					

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

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.

On 30 November 2020, the pharmaceutical company submitted a dossier for the benefit assessment of tezacaftor/ivacaftor to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 30 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 tezacaftor/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 G-BA website on 1 March 2021. The deadline for submitting the written statements was 22 March 2021.

The oral hearing was held on 06 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 meetings.

The evaluation of the written statements received and the oral hearing were discussed at the meeting of the subcommittee on 11 May 2021, and the draft resolution was approved.

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

Chronological course of consultation

Meeting	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	06 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

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

Prof. Hecken