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
Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir alafenamide
(New therapeutic indication: HIV infection, 2 to < 6 years)

of 20 April 2023

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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 online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The combination of active ingredients elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide (Genvoya) was listed for the first time on 1 January 2016 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 3 October 2022, Gilead Sciences 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, 12.12.2008, sentence 7).

On 28 October 2022, 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 elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide with the new therapeutic indication (children with HIV-1 infection aged 2 to < 6 years) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 February 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure.

The oral hearing has been dispensed with since all assessment experts who submitted written statements waived their right to make an oral statement.

The G-BA came to a resolution on whether an additional benefit of elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide compared to 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 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 elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide. In the light of the above, and taking into account the statements received, 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 Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir alafenamide (Genvoya) according to the product information

Genvoya is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in adults and paediatric patients aged from 2 years and with body weight at least 14 kg.

Therapeutic indication of the resolution (resolution of 20.04.2023):

Genvoya is indicated for the treatment of infection with HIV-1 without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in children aged 2 to < 6 years and weighing at least 14 kg.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Therapy-naive children with HIV-1 infection aged 2 to < 6 years without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir

Abacavir + lamivudine or abacavir + emtricitabine, in each case in combination with
- dolutegravir or
- lopinavir/ ritonavir or
- raltegravir or
- nevirapine or

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

- atazanavir/ ritonavir or
- darunavir/ ritonavir

b) Therapy-experienced children with HIV-1 infection aged 2 to < 6 years without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir

- A patient-individual antiretroviral therapy using a selection of approved active ingredients; taking into account the previous therapy/ therapies and the reason for the change of therapy, in particular, therapy failure because of virological failure and the possible associated development of resistance or because of side effects

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. In the present therapeutic indication, besides elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide, the following active ingredients are generally approved for the treatment of HIV-1 infection in children aged 2 to < 6 years (taking into account any approved age restrictions):

Protease inhibitors (PI): Lopinavir/ ritonavir, atazanavir, ritonavir, tipranavir, darunavir (in combination with ritonavir 3 years and older)

Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI): Abacavir, lamivudine, zidovudine, emtricitabine, tenofovir disoproxil, didanosine

Non-nucleoside reverse transcriptase inhibitors (NNRTI): Nevirapine, efavirenz, etravirine

Integrase inhibitors (INI): Dolutegravir, raltegravir

Other antivirals: Maraviroc (entry inhibitor)

on 2. A non-medicinal treatment is unsuitable as a comparator therapy in this therapeutic indication.

on 3. In the present therapeutic indication, a resolution of the G-BA on the benefit assessment of active ingredients according to Section 35a SGB V for the treatment of HIV-1 infection in children aged 4 weeks to < 6 years was passed for the active ingredient dolutegravir on 15 July 2021, amended by resolutions of 18 March 2022 and 6 October 2022.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as 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.

For the treatment of HIV-1 infections in children aged 2 to < 6 years, the active ingredients mentioned under 1. are available according to the respective approved therapeutic indication. The systematic literature search identified a World Health Organization guideline from 2018[2] and its update from 2019[3] and the German-Austrian S2k guideline on anti-retroviral therapy of HIV infection in children and adolescents from 2019[4].

Despite methodological limitations, the S2k guideline has a special significance for the German healthcare context. For children aged 2 to < 6 years with HIV-1, only the German-Austrian S2k guideline describes the resistance situation in the German healthcare context. In addition, the recommendations of the scientific-medical societies for the individual age categories are consistent with those of the S2K guideline. The recommendations of the German-Austrian S2k guideline are therefore used to determine the appropriate comparator therapy.

The S2K guideline recommends an ART regimen as base therapy for therapy-naive patients with HIV-1 infection aged 2 to < 6 years, which is composed of two NRTIs and a third component from either the PI, NNRTI or INI product class. Unless there is primary resistance or the patient is a carrier of the HLA-B*5701 gene, a combination of the NRTIs abacavir and lamivudine is recommended as the first choice, as these are superior to the other NRTIs in terms of anti-retroviral efficacy and side effects. In addition, a combination of abacavir with emtricitabine is recommended as an alternative. As a third part of the combination therapy, several product classes and active ingredients are approved.

The German-Austrian S2k guideline recommends the active ingredients raltegravir, nevirapine and lopinavir boosted with ritonavir, atazanavir and darunavir. The active ingredient dolutegravir is recommended by the German-Austrian S2k guideline from the age of 6 years. In German medical treatment practice, dolutegravir is already administered from the age of 2 years.

In the overall assessment, a combination therapy of abacavir and lamivudine or abacavir and emtricitabine with dolutegravir or raltegravir or nevirapine or lopinavir/ ritonavir or atazanavir/ ritonavir or darunavir/ ritonavir is to be therefore considered

[2] World Health Organization (WHO). Updated recommendations on first-line and second-line anti-retroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidance [online]. Geneva (SUI): WHO Press; 2018.

[3] World Health Organization (WHO). Update of recommendations on first- and second-line anti-retroviral regimens: policy brief [online]. Geneva (SUI): WHO Press; 2019.

[4] German-Austrian guidelines on antiretroviral therapy of HIV infection in children and adolescents [online]. AWMF register number 048-011. Berlin (GER): Association of the Scientific Medical Societies (AWMF); 2019.

equally appropriate for therapy-naive children with HIV-1 infection aged 2 to < 6 years who have neither currently nor in the past shown to be resistant to the class of integrase inhibitors, emtricitabine or tenofacetin.

When determining the appropriate comparator therapy for therapy-experienced children aged 2 to < 6 years with HIV-1 infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir, the search for evidence revealed that after one or more prior therapies, depending on the active ingredients/ product classes used and the reason for the change in therapy (e.g. therapy failure, side effects), a patient-individual pharmacotherapy coordinated with the treated subject is recommended. The naming of a defined combination of active ingredients in the sense of a therapy standard after therapy failure cannot be deduced based on the evidence available and because of the patient-individual selection of the therapy scheme depending on the previous therapy. In principle, all possible combinations of active ingredients can therefore be regarded as appropriate.

In both therapy-naive and therapy-experienced children with HIV-1 infection, the use of the medicinal products in compliance with the marketing authorisation, in particular the age-appropriate use, must be observed.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide is assessed as follows:

An additional benefit is not proven for therapy-naive and therapy-experienced children with HIV-1 infection aged 2 to < 6 years, without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir.

Justification:

The pharmaceutical company does not present direct comparator data of elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide in the present therapeutic indication compared to the specific appropriate comparator therapy for both therapy-naive and therapy-experienced children with HIV-1 infection aged 2 to < 6 years.

In addition, the pharmaceutical company presents the single-arm, label-enabling study GS-US-292-0106, which was conducted in two cohorts.

The single-arm study is unsuitable for the assessment of an additional benefit due to the lack of comparison with the appropriate comparator therapy.

Overall, on the basis of the GS-US-292-0106 study, no additional benefit over the appropriate comparator therapy can be derived for both treatment-naive and treatment-experienced children with HIV-1 infection aged 2 to < 6 years, without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the combination of active ingredients elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide (Genvoya®).
Genvoya is indicated for the treatment of infection with HIV-1 without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in children aged 2 to < 6 years and weighing at least 14 kg.

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Therapy-naive children with HIV-1 infection aged 2 to < 6 years without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir

The G-BA determined abacavir with lamivudine or abacavir with emtricitabine, each in combination with dolutegravir, lopinavir/ ritonavir, raltegravir, nevirapine, atazanavir/ ritonavir or darunavir/ ritonavir to be the appropriate comparator therapy.

In addition, the pharmaceutical company presents the single-arm, label-enabling study GS-US-292-0106, which was conducted in two cohorts.

Overall, 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 elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide compared with the appropriate comparator therapy.

An additional benefit is therefore not proven.

b) Therapy-experienced children with HIV-1 infection aged 2 to < 6 years without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir

The G-BA determined an appropriate comparator therapy to be a patient-individual antiretroviral therapy using a selection of approved active ingredients taking into account the previous therapy/ therapies and the reason for the change of therapy, in particular therapy failure because of virological failure and the possible associated development of resistance or because of side effects.

In addition, the pharmaceutical company presents the single-arm, label-enabling study GS-US-292-0106, which was conducted in two cohorts.

Overall, 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 elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide compared with the appropriate comparator therapy.

An additional benefit is therefore not proven.

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

The number of patients based on a query by the pharmaceutical company of the reporting cases submitted to the Robert Koch Institute (RKI) in accordance with the Infection Protection Act from the SurvStat@RKI2.05 database is 21 children aged ≥ 2 to < 6 years who were

[5] Robert Koch Institute. Query parameter SurvStat@RKI 2.0, query date 08.08.2022 [online]. URL: https://survstat.rki.de/

infected with HIV in 2022. In addition, the pharmaceutical company makes assumptions about the pretreated and non-pretreated children as well as the existing resistance situation. Based on data from the Federal Health Reporting, 87.8% of the population has statutory health insurance.
The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainties due to the limited epidemiological data basis, particularly with regard to additional reports submitted to the RKI compared to the data status used and the lack of consideration of deaths, the lack of restriction to body weight and due to uncertainties in the calculation of the percentage of patients with existing resistance to the class of integrase inhibitors, emtricitabine or tenofovir.
This results in a number of approx. 3 therapy-naive and approx. 13 therapy-experienced children infected with HIV-1 aged 2 to < 6 years for the SHI 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 product characteristics, SmPC) for Genvoya (combination of active ingredients: elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide) at the following publicly accessible link (last access: 14 December 2022):

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

Treatment with elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide should only be initiated and monitored by doctors experienced in treating patients with HIV-1.

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 April 2023).

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.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

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 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.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body

measurements of the population" were applied. [6] For active ingredients that are dosed depending on body weight, standard patients with an average body weight of approx. 14 kg (for patients aged 2 to under 3 years) or approx. 21 kg (for patients aged 5 to under 6 years) are used as the basis for calculating costs. The average body height (2 to < 6 years) is 0.93 - 1.15 m. Therefore, an average body surface area of 0.59 - 0.82 m² (calculation according to Du Bois 1916) results for children aged 2 to < 6 years.

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				
Elvitegravir/ cobicistat/ Emtricitabine/ tenofovir alafenamide	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
a) Therapy-naive children with HIV-1 infection aged 2 to < 6 years				
Base therapy				
Abacavir	Continuously, 1 x daily or 2 x daily	365	1	365
Emtricitabine	Continuously, 1 x daily	365	1	365
Lamivudine	Continuously, 1 x daily or 2 x daily	365	1	365
3. Concomitant active ingredient for the above-mentioned base therapy				
Atazanavir	Continuously, 1 x daily	365	1	365
+ ritonavir	Continuously, 1 x daily	365	1	365
Darunavir	Continuously, 1 x daily	365	1	365
+ ritonavir	Continuously, 1 x daily	365	1	365
Dolutegravir	Continuously, 1 x daily	365	1	365
Lopinavir/ ritonavir	Continuously, 2 x daily	365	1	365

[6] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Nevirapine	Continuously, 2 x daily	365	1	365
Raltegravir	Continuously, 2 x daily	365	1	365
b) Therapy-experienced children with HIV-1 infection aged 2 to < 6 years				
Abacavir + lamivudine + lopinavir/ ritonavir				
Abacavir	Continuously, 1 x daily or 2 x daily	365	1	365
Lamivudine	Continuously, 1 x daily or 2 x daily	365	1	365
Lopinavir/ ritonavir	Continuously, 2 x daily	365	1	365
Abacavir + lamivudine + atazanavir + ritonavir				
Abacavir	Continuously, 1 x daily or 2 x daily	365	1	365
Lamivudine	Continuously, 1 x daily or 2 x daily	365	1	365
Atazanavir + ritonavir	Continuously, 1 x daily Continuously, 1 x daily	365 365	1 1	365 365

Consumption:

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up to the next higher available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

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					
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide	90 mg/ 90 mg/ 120 mg/ 6 mg	90 mg/ 90 mg/ 120 mg/ 6 mg	1 x 90 mg/ 90 mg/ 120 mg/ 6 mg	365	365 x 90 mg/ 90 mg/ 120 mg/ 6 mg
Appropriate comparator therapy					
a) Therapy-naive children with HIV-1 infection aged 2 to < 6 years					
Base therapy					
Abacavir LSE (20 mg/ml)	<u>16 mg/kg:</u> 224 - 336 mg or <u>8 mg/kg:</u> 112 - 168 mg	224 - 336 mg	1 x 240 mg = 1 x 12.0 ml - 1 x 340 mg = 1 x 17.0 ml or 2 x 120 mg = 2 x 6.0 ml - 2 x 180 mg = 2 x 9.0 ml	365	365 x 12.0 ml - 17.0 ml or 730 x 6.0 ml - 9.0 ml
Emtricitabine LSE (10 mg/ml)	<u>6 mg/kg</u> 84 - 126 mg	84 - 126 mg	1 x 90 mg = 1 x 9 ml - 1 x 130 mg = 1 x 13.0 ml	365	365 x 9.0 ml - 13.0 ml
Lamivudine LSE (10 mg/ml)	<u>10 mg/kg:</u> 140 - 210 mg or <u>5 mg/kg:</u> 70 - 105 mg	140 - 210 mg	1 x 140 mg = 1 x 14 ml - 1 x 210 mg = 1 x 21 ml or 2 x 70 mg = 2 x 7 ml - 2 x 110 mg = 2 x 11.0 ml	365	365 x 14.0 ml - 21 ml or 730 x 7.0 ml - 11.0 ml
3. Concomitant active ingredient for the above-mentioned base therapy					
Atazanavir POS (50 mg) + Ritonavir POS (100 mg)	<u>< 15 kg:</u> 200 mg <u>≥ 15 kg:</u> 250 mg + 80 mg	200 mg 250 mg + 80 mg	4 x 50 mg 5 x 50 mg + 1 x 100 mg	365 365	1,460 x 50 mg - 1825 x 50 mg + 365 x 100 mg
Darunavir	<u>≥ 15 kg</u>				

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient / year	Average annual consumption by potency
SUS (100 mg/ml) + Ritonavir POS (100 mg)	600 mg + 80 mg	600 mg + 80 mg	1 x 600 mg + 1 x 100 mg	365 365	365 x 600 mg + 365 x 100 mg
Dolutegravir TOS (5 mg)	14 to < 20 kg: 25 mg ≥ 20 kg: 30 mg	25 mg - 30 mg	5 x 5 mg - 6 x 5 mg	365	1825 x 5 mg - 2190 x 5 mg
Lopinavir/ ritonavir OS (80/20) mg/ml	BSA 0.50 - 0.80 m^2 115/28.8 mg - 184/46 mg	230/57.6 mg = 2.8 ml - 368/92 mg = 4.6 ml	2 x 115/28.8 mg = 2 x 1.4 ml - 2 x 184/46 mg = 2 x 2.3 ml	365	730 x 1.4 ml - 730 x 2.3 ml
Nevirapine SUS (10 mg/ml)	12.5 kg - 23.21 kg 100 mg - 150 mg	200 mg - 300 mg	2 x 100 mg - 2 x 150 mg	365	730 x 100 mg - 730 x 150 mg
Raltegravir GSO (10 mg/ml) CT (25 mg) or (100 mg)	14 - < 20 kg 100 mg ≥ 20 kg 150 mg	200 mg - 300 mg	2 x 100 mg - 2 x 100 mg + 4 x 25 mg	365	730 x 100 mg - 730 x 100 mg + 1460 x 25 mg
b) Therapy-experienced children with HIV-1 infection aged 2 to < 6 years					
Abacavir + lamivudine + lopinavir/ ritonavir					
Abacavir LSE (20 mg/ml)	16 mg/kg: 224 mg or 8 mg/kg: 112 mg	224 mg	1 x 240 mg = 1 x 12.0 ml or 2 x 120 mg = 2 x 6.0 ml	365	365 x 12.0 ml or 730 x 6.0 ml
Lamivudine LSE (10 mg/ml)	10 mg/kg: 140 mg or 5 mg/kg: 70 mg	140 - mg	1 x 140 mg = 1 x 14 ml or 2 x 70 mg = 2 x 7 ml	365	365 x 14.0 ml or 730 x 7.0 ml

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient / year	Average annual consumption by potency
Lopinavir/ ritonavir OS (80/20) mg/ml	BSA 0.50 m^2 115/28.8 mg	230/57.6 mg = 2.8 ml	2 x 115/28.8 mg = 2 x 1.4 ml	365	730 x 1.4 ml
Abacavir + lamivudine + atazanvir + ritonavir					
Abacavir LSE (20 mg/ml)	16 mg/kg: 336 mg or 8 mg/kg: 168 mg	336 mg	1 x 340 mg = 1 x 17.0 ml or 2 x 180 mg = 2 x 9.0 ml	365	365 x 17.0 ml or 730 x 9.0 ml
Lamivudine LSE (10 mg/ml)	10 mg/kg: 210 mg or 5 mg/kg: 105 mg	210 mg	1 x 210 mg = 1 x 21 ml or 2 x 110 mg = 2 x 11.0 ml	365	365 x 21 ml or 730 x 11.0 ml
Atazanavir POS (50 mg) + ritonavir POS (100 mg)	≥ 15 kg: 250 mg + 80 mg	250 mg + 80 mg	5 x 50 mg + 1 x 100 mg	365	1825 x 50 mg + 365 x 100 mg

Costs:

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					
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide 90 mg/ 90 mg/ 120 mg/ 6 mg	90 FCT	€ 2,714.32	€ 2.00	€ 260.10	€ 2,452.22
Appropriate comparator therapy					
a) Therapy-naive children with HIV-1 infection aged 2 to < 6 years					
Abacavir 20 mg/ml	240 ml OS	€ 126.09	€ 2.00	€ 14.53	€ 109.56
Atazanavir 50 mg	30 POS	€ 163.91	€ 2.00	€ 14.49	€ 147.42
Darunavir 100 mg/ml	200 ml SUS	€ 774.59	€ 2.00	€ 72.45	€ 700.14

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
Dolutegravir 5 mg	60 TOS	€ 145.37	€ 2.00	€ 5.30	€ 138.07
Emtricitabine 10 mg/ml	170 ml LSE	€ 92.69	€ 2.00	€ 7.73	€ 82.96
Lamivudine 10 mg/ml	240 ml LSE	€ 64.26	€ 2.00	€ 6.70	€ 55.56
Lopinavir/ ritonavir 80/20 mg/ml	5 x 60 ml OS	€ 827.97	€ 2.00	€ 103.36	€ 722.61
Nevirapine 10 mg/ml	240 ml SUS	€ 116.18	€ 2.00	€ 9.96	€ 104.22
Raltegravir 100 mg	60 GOS	€ 229.75	€ 2.00	€ 20.74	€ 207.01
Raltegravir 100 mg	60 CT	€ 229.75	€ 2.00	€ 20.74	€ 207.01
Raltegravir 25 mg	60 CT	€ 65.90	€ 2.00	€ 5.18	€ 58.72
Ritonavir 100 mg	30 POS	€ 64.97	€ 2.00	€ 6.80	€ 56.17
b) Therapy-experienced children with HIV-1 infection aged 2 to < 6 years					
Abacavir 20 mg/ml	240 ml LSE	€ 126.09	€ 2.00	€ 14.53	€ 109.56
Atazanavir 50 mg	30 POS	€ 163.91	€ 2.00	€ 14.49	€ 147.42
Lamivudine 10 mg/ml	240 ml LSE	€ 64.26	€ 2.00	€ 6.70	€ 55.56
Lopinavir/ ritonavir 80/20 mg/ml	5 x 60 ml OS	€ 827.97	€ 2.00	€ 103.36	€ 722.61
Ritonavir 100 mg	30 POS	€ 64.97	€ 2.00	€ 6.80	€ 56.17
Abbreviations: FCT = film-coated tablets; GOS = granules for oral suspension; OS = oral solution ; CT = chewable tablets; BSA = body surface area; POS = powder for oral suspension; TOS = tablet for oral suspension; SUS = suspension					

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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.

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir alafenamide

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination

therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 21 December 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy. A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 24 May 2022.

On 28 October 2022, the pharmaceutical company submitted a dossier for the benefit assessment of elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 31 October 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide.

The dossier assessment by the IQWiG was submitted to the G-BA on 24 January 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 February 2023. The deadline for submitting written statements was 22 February 2023.

The oral hearing has been dispensed with since all assessment experts who submitted written statements waived their right to make an oral statement.

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 was discussed at the session of the subcommittee on 11 April 2023, and the proposed resolution was approved.

At its session on 20 April 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	21 December 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	24 May 2022	New implementation of the appropriate comparator therapy
Working group Section 35a	1 March 2023	Information on written statements received; preparation of the oral hearing
Working group Section 35a	15 March 2023 5 April 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	13 April 2023	Concluding discussion of the draft resolution
Plenum	20 April 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 April 2023

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

Prof. Hecken