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 Bictegravir/ emtricitabine/ tenofovir alafenamide (new therapeutic indication: HIV-1 infection, 2 to < 18 years)

of 15 June 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The combination of active ingredients bictegravir/ emtricitabine/ tenofovir alafenamide (Biktarvy) was listed for the first time on 1 July 2018 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 21 November 2022, Biktarvy 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 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, sentence 7).

On 19 December 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

bictegravir/ emtricitabine/ tenofovir alafenamide with the new therapeutic indication "for the treatment of human immunodeficiency virus-1 (HIV-1) infection in paediatric patients aged from 2 to < 18 years and weighing at least 14 kg" 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 03 April 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 a written statement waived their right to make an oral statement.

The G-BA came to a resolution on whether an additional benefit of bictegravir/ 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 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 bictegravir/ emtricitabine/ tenofovir alafenamide.

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 Bictegravir/ emtricitabine/ tenofovir alafenamide (Biktarvy) according to the product information

Biktarvy is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and paediatric patients at least 2 years of age and weighing at least 14 kg without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.

Therapeutic indication of the resolution (resolution of 15 June 2023):

Biktarvy is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in paediatric patients aged 2 to < 18 years and weighing at least 14 kg g without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Therapy naive children with HIV-1 infection aged 2 to < 6 years without past or present evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir

Appropriate comparator therapy for bictegravir/ emtricitabine/ tenofovir alafenamide

Abacavir + lamivudine or abacavir + emtricitabine, in each case in combination with

- dolutegravir or
- lopinavir/ ritonavir or
- raltegravir or
- nevirapine or
- atazanavir + ritonavir or
- darunavir + ritonavir

b) Therapy naive children with HIV-1 infection aged 6 to < 12 years without past or present evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir

Appropriate comparator therapy for bictegravir/ emtricitabine/ tenofovir alafenamide

Abacavir + lamivudine or abacavir + emtricitabine, in each case in combination with

- dolutegravir or
- atazanavir + ritonavir or
- darunavir + ritonavir

c) Therapy naive adolescents with HIV-1 infection aged 12 to < 18 years without past or present evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir

Appropriate comparator therapy for bictegravir/ emtricitabine/ tenofovir alafenamide

Tenofovir alafenamide + emtricitabine or abacavir + lamivudine or abacavir + emtricitabine, each in combination with

- dolutegravir or
- atazanavir + ritonavir or
- darunavir + ritonavir or
- elvitegravir/ cobicistat

d) Therapy experienced children and adolescents with HIV-1 infection aged 2 to < 18 years without past or present evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir

Appropriate comparator therapy for bictegravir/ emtricitabine/ tenofovir alafenamide

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 bictegravir/ emtricitabine/ tenofovir alafenamide, the following active ingredients are generally approved for the treatment

of HIV-1 infection in children aged 2 to < 18 years (taking into account any approved age restrictions):

Protease inhibitors (PI): lopinavir (from 2 weeks), atazanavir (from 3 months), ritonavir (from 2 years), tipranavir (from 2 years), darunavir (from 3 years in combination with ritonavir), fosamprenavir (from 6 years)

Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI): abacavir, lamivudine, zidovudine, emtricitabine (from 4 months), tenofovir disoproxil (from 2 years), tenofovir alafenamide (from 12 years), didanosine

Non-nucleoside reverse transcriptase inhibitors (NNRTI): nevirapine, efavirenz (from 3 months), etravirine (from 2 years), rilpivirine (from 12 years), doravirine (from 12 years)

Integrase inhibitors (INI): raltegravir (from 4 weeks), dolutegravir (from 4 weeks), elvitegravir (from 2 years)

Other antivirals: maraviroc (fusion inhibitor; from 2 years), enfuvirtide (fusion inhibitor; from 6 years)

Other therapeutic agents: cobicistat (pharmacokinetic enhancer; from 12 years)

on 2. A non-medicinal treatment cannot be considered in the present therapeutic indication.

on 3. Resolutions on procedures according to Section 35a SGB V in the present therapeutic indication for children and adolescents:

Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide (nAWG) (resolution of 20 April 2022)

Doravirine (nAWG) (resolution of 20 October 2022)

Doravirine/ lamivudine/ tenofovir disoproxil (nAWG) (resolution of 20 October 2022)

Dolutegravir *(resolution of 15 July 2021)*

Cobicistat *(resolution of 1 October 2020)*

Dolutegravir/ lamivudine *(resolution of 6 February 2020)*

Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide (nAWG) *(resolution of 5 July 2018)*

Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil (nAWG) *(resolution of 3 May 2018)*

Darunavir/ cobicistat/ emtricitabine/ tenofovir alafenamide *(resolution of 16 March 2018)*

Dolutegravir (nAWG) *(resolution of 21 September 2017)*

Rilpivirine/ emtricitabine/ tenofovir alafenamide *(resolution of 5 January 2017)*

Emtricitabine/ tenofovir alafenamide *(resolution of 3 November 2016)*

Rilpivirine (nAWG) *(resolution of 16 June 2016)*

Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide *(resolution of 16 June 2016)*

Dolutegravir/ abacavir/ lamivudine *(resolution of 19 March 2015)*

Dolutegravir *(resolution of 7 August 2014)*

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 and adolescents aged 2 to < 18 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 antiretroviral 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 and adolescents aged 2 to < 18 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.

<u>Therapy naive children aged 2 to < 6 years</u>

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

[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.

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 each with dolutegravir or raltegravir or nevirapine or lopinavir/ ritonavir or atazanavir + ritonavir or darunavir + ritonavir is to be therefore considered 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 tenofovir.

Therapy naive children aged 6 to < 12 years

The S2K guideline recommends an ART regimen as base therapy for therapy-naive patients with HIV-1 infection aged 6 to < 12 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 protein inhibitors atazanavir or darunavir boosted with ritonavir and the integrase inhibitor dolutegravir are recommended as a third concomitant active ingredient in the German-Austrian S2k guideline.

In the overall assessment, a combination therapy of abacavir and lamivudine or abacavir and emtricitabine each with the protein inhibitors atazanavir or darunavir boosted with ritonavir or the integrase inhibitor dolutegravir is to be therefore considered equally appropriate for therapy-naive children with HIV-1 infection aged 6 to < 12 years who have neither currently nor in the past shown to be resistant to the class of integrase inhibitors, emtricitabine or tenofovir.

Therapy naive adolescents aged 12 to < 18 years

For therapy naive adolescents from the age of 12 years, the evidence search showed that the nucleosidal and nucleotidal inhibitors of the reverse transcriptase tenofovir disoproxil or tenofovir alafenamide plus emtricitabine or abacavir plus lamivudine or abacavir plus emtricitabine as NRTI backbone show very good efficacy with a favourable

risk profile. In addition, these are active ingredients and combinations of active ingredients for which extensive published data are available. However, tenofovir disoproxil should be used in non-pretreated adolescents from the age of 12 years only if the use of first-line medicinal products is excluded because of resistance to NRTI or intolerance. Tenofovir disoproxil is therefore out of the question when determining the appropriate comparator therapy for therapy naive adolescents aged 12 years and older. In the overall assessment, based on the available evidence, tenofovir alafenamide plus emtricitabine, abacavir plus lamivudine and abacavir plus emtricitabine are considered equally appropriate NRTI backbones in the context of the appropriate comparator therapy. Based on the available evidence, the protein inhibitors atazanavir or darunavir boosted with ritonavir and the integrase inhibitor elvitegravir boosted with cobicistat as well as the integrase inhibitor dolutegravir are determined as equally appropriate concomitant active ingredients for the appropriate comparator therapy. The choice of the active ingredients atazanavir + ritonavir, darunavir + ritonavir, elvitegravir/ cobicistat and dolutegravir as concomitant active ingredients is justified by the scope, genuineness and quality of the underlying body of evidence. Overall, tenofovir alafenamide plus emtricitabine or abacavir plus lamivudine or abacavir plus emtricitabine, each in combination with atazanavir + ritonavir or darunavir + ritonavir or elvitegravir/ cobicistat or dolutegravir is determined as the appropriate comparator therapy for therapy-naive adolescents with HIV infection aged 12 to < 18 years who have neither currently nor in the past shown to be resistant to the class of integrase inhibitors, emtricitabine or tenofovir.

Therapy experienced children and adolescents aged 2 to < 18 years

When determining the appropriate comparator therapy for therapy-experienced children and adolescents with HIV-1 infection aged 2 to < 18 years who have neither currently nor in the past shown to be resistant to the class of integrase inhibitors, emtricitabine or tenofovir, the evidence search 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 and adolescents 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 mandate.

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 bictegravir/ emtricitabine/ tenofovir alafenamide is assessed as follows:

An additional benefit is not proven for children and adolescents with HIV-1 infection aged 2 to < 18 years, who have neither currently nor in the past shown to be resistant to the class of integrase inhibitors, emtricitabine or tenofovir.

Justification:

The pharmaceutical company does not present direct comparator data of bictegravir/ emtricitabine/ tenofovir alafenamide in the present therapeutic indication compared to the specific appropriate comparator therapy for both therapy-naive and therapy-experienced children and adolescents with HIV-1 infection aged 2 to < 18 years.

In addition, the pharmaceutical company presents the single-arm, label-enabling study GS1474.

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 GS1474 study, no additional benefit over the appropriate comparator therapy can be derived for both treatment-naive and treatment-experienced children and adolescents with HIV-1 infection aged 2 to < 18 years, who have neither currently nor in the past shown to be resistant to the class of integrase inhibitors, 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 bictegravir/ emtricitabine/ tenofovir alafenamide (Biktarvy).

Biktarvy is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in paediatric patients aged 2 to < 18 years and weighing at least 14 kg g without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.

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

a) Therapy naive children with HIV-1 infection aged 2 to < 6 years without past or present evidence of viral 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 or nevirapine or atazanavir + ritonavir or darunavir + ritonavir to be the appropriate comparator therapy for bictegravir/ emtricitabine/ tenofovir alafenamide.

In addition, the pharmaceutical company presents the single-arm, label-enabling study GS1474.

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 bictegravir/ emtricitabine/ tenofovir alafenamide compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

b) Therapy naive children with HIV-1 infection aged 6 to < 12 years without past or present evidence of viral 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 or atazanavir + ritonavir or darunavir + ritonavir to be the appropriate comparator therapy for bictegravir/ emtricitabine/ tenofovir alafenamide.

In addition, the pharmaceutical company presents the single-arm, label-enabling study GS1474.

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 bictegravir/ emtricitabine/ tenofovir alafenamide compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

c) Therapy naive adolescents with HIV-1 infection aged 12 to < 18 years without past or present evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir

The G-BA determined tenofovir alafenamide with emtricitabine or abacavir with emtricitabine or abacavir with lamivudine, each in combination with dolutegravir or atazanavir + ritonavir or darunavir + ritonavir or elvitegravir/ cobicistat to be the appropriate comparator therapy for bictegravir/ emtricitabine/ tenofovir alafenamide.

In addition, the pharmaceutical company presents the single-arm, label-enabling study GS1474.

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 bictegravir/ emtricitabine/ tenofovir alafenamide compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

d) Therapy experienced children and adolescents with HIV-1 infection aged 2 to < 18 years without past or present evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir

The G-BA determined an appropriate comparator therapy for bictegravir/ emtricitabine/ tenofovir alafenamide to be a patient-individual anti-retroviral therapy using a selection of approved active ingredients taking into account the previous therapy(ies) 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 GS1474.

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 bictegravir/ 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

Children and adolescents with HIV-1 aged 2 to < 18 years without past or present evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir

The number of patients is the target population in statutory health insurance (SHI). The information is based on patient numbers based on the information provided by the pharmaceutical company in the dossier.

The number of patients based on the pharmaceutical company's query of the reported cases from the SurvStat@RKI2.0[5] database submitted to the Robert Koch Institute (RKI) in accordance with the Infection Protection Act is 182 children and adolescents aged ≥ 2 to < 18 years who were infected with HIV in 2022. In addition, the pharmaceutical company makes assumptions about the pretreated and non-pretreated children and adolescents 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, restriction of patients with an eGFR ≥ 30 ml/min and due to uncertainties in the calculation of the percentage of patients with existing resistance to the class of integrase inhibitors, emtricitabine or tenofovir. On the basis of the available data, no reliable statement can be made as to whether the stated patient numbers are an overestimate or an underestimate.

Overall, the following patient numbers result for therapy-naive children and adolescents in the SHI target population for the respective age categories: 2 to < 6 years approx. 2 patients,

[5] Robert Koch Institute. Query parameter SurvStat@RKI 2.0, query date 08.11.2022 [online]. URL: https://survstat.rki.de/

6 to < 12 years approx. 10 patients, 12 to < 18 years approx. 22 patients. For therapy-experienced children and adolescents in the SHI target population aged 2 to < 18 years, this results in approx. 150 patients.

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 Biktarvy (active ingredient: bictegravir/ emtricitabine/ tenofovir alafenamide) at the following publicly accessible link (last access: 28 February 2023):

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

Treatment with bictegravir/ 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: 15 May 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 14.1 kg (for children aged 2 to under 3 years) or 20.8 kg (for children 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 - 0.81 m² (calculation according to Du Bois 1916) results for children aged 2 to < 6 years.

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

For children aged 6 to under 12 years, the official representative statistics for the cost calculation result in an average body weight of 23.6 kg (for children aged 6 to under 7 years) and 42.1 kg (for children aged 11 to under 12 years).

In this particular patient population, it is up to the physician to decide which is the most appropriate dosage form for the respective child from 2 years < 6 years of age, depending on body weight or body surface area and dose. For this reason, where available, the dosages of both a solid (film-coated tablet or hard capsule) and a liquid formulation (solution or suspension) are shown for each active ingredient.

If more than one treatment mode was indicated in the product information, "once daily" was calculated for better comprehensibility.

Treatment period:

a) Therapy-naive children with HIV-1 infection aged 2 to < 6 years

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Bictegravir/ emtricitabine/ tenofovir alafenamide	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Dolutegravir or lopinavir/ ritonavir or raltegravir or nevirapine or atazanavir + ritonavir or darunavir + ritonavir in each case in combination with the base therapy (abacavir + lamivudine or abacavir + emtricitabine)				
Base therapy (2 x NRTI: abacavir + lamivudine or abacavir + emtricitabine)				
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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
+ 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
Nevirapine	Continuously, 2 x daily	365	1	365
Raltegravir	Continuously, 2 x daily	365	1	365

b) Therapy-naive children with HIV-1 infection aged 6 to < 12 years

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Bictegravir/ emtricitabine/ tenofovir alafenamide	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Abacavir + lamivudine or abacavir + emtricitabine each in combination with - dolutegravir or atazanavir + ritonavir or darunavir + ritonavir				
Base therapy (2 x NRTI: abacavir + lamivudine or abacavir + emtricitabine)				
Abacavir	Continuously, 1 x daily or 2 x daily	365	1	365
Emtricitabine	Continuously, 1 x daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Lamivudine	Continuously, 1 x daily or 2 x daily	365	1	365
Abacavir/ lamivudine	Continuously, 1 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 or 2 x daily	365	1	365

c) Therapy-naive adolescents with HIV-1 infection aged 12 to < 18 years

Currently, elvitegravir in combination with cobicistat is only available on the German market as a combination medicinal product with emtricitabine/ tenofovir alafenamide. It is therefore not possible to present the costs of the individual active ingredient.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Bictegravir/ emtricitabine/ tenofovir alafenamide	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Tenofovir alafenamide + emtricitabine or abacavir + lamivudine or abacavir + emtricitabine each in combination with dolutegravir or atazanavir + ritonavir or darunavir + ritonavir or elvitegravir/ cobicistat				
Base therapy (2 x NRTI: abacavir + lamivudine or abacavir + emtricitabine)				
Abacavir	Continuously, 1 x daily or 2 x daily	365	1	365
Abacavir/ lamivudine	Continuously, 1 x daily	365	1	365
Emtricitabine	Continuously, 1 x daily	365	1	365
Emtricitabine/ tenofovir alafenamide	Continuously, 1 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 or 2 x daily	365	1	365
Fixed combination of base therapy and concomitant active ingredient				
Emtricitabine/ tenofovir alafenamide + elvitegravir/ cobicistat	Continuously, 1 x daily	365	1	365

d) Therapy-experienced children and adolescents with HIV-1 infection aged 2 to < 18 years

Because of the different combination options in patient-individual therapy, not all possible variants of combination therapies are presented and considered but the cost range from a

cost-effective (emtricitabine/ tenofovir disoproxil + nevirapine) to a cost-intensive therapy (abacavir + emtricitabine + enfuvirtide) is specified as an example.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Bictegravir/ emtricitabil/ tenofovir alafenamide	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
A patient-individual antiretroviral therapy with selection of approved active ingredients				
Abacavir	Continuously, 2 x daily	365	1	365
Emtricitabine	Continuously 1 x daily	365	1	365
Nevirapine	Continuously, 2 x daily	365	1	365
Emtricitabine/ tenofovir disoproxil	Continuously, 1 x daily	365	1	365
Enfuvirtide	Continuously, 2 x daily	365	1	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.

a) Therapy-naive children with HIV-1 infection aged 2 to < 6 years

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					
Bictegravir/ emtricitabine/ tenofovir alafenamide	30 mg/ 120 mg/ 15 mg	30 mg/ 120 mg/ 15 mg	1 x 30 mg/ 120 mg/ 15 mg	365	365 x 30 mg/ 120 mg/ 15 mg
Appropriate comparator therapy					
Base therapy (2 x NRTI: abacavir + lamivudine or abacavir + emtricitabine)					
Abacavir OS (20 mg/ml)	16 mg/kg: 225.6 - 332.8 mg	225.6 - 332.8 mg	1 x 240 mg = 1 x 12.0 ml - 1 x 340 mg = 1 x 17.0 ml	365	365 x 12.0 ml - 17.0 ml
Abacavir FCT (300 mg)	< 25 kg: 450 mg	450 mg	1.5 x 300 mg	365	547.5 x 300 mg
Emtricitabine OS (10 mg/ml)	6 mg/kg 84.6 - 124.8 mg	84.6 - 124.8 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 OS (10 mg/ml)	10 mg/kg: 141 - 208 mg	141 - 208 mg	1 x 140 mg = 1 x 14 ml - 1 x 210 mg = 1 x 21 ml	365	365 x 14.0 ml - 21 ml
Lamivudine FCT (150 mg)	14 - 20 kg 150 mg 20 - 25 kg 225 mg	150 - 225 mg	1 x 150 mg - 1.5 x 150 mg	365	365 x 150 mg - 547.5 x 150 mg
3. Concomitant active ingredient for the above-mentioned base therapy					
Atazanavir POS (50 mg) + Ritonavir POS (100 mg)	< 15 kg: 200 mg ≥ 15 kg: 250 mg + 80 mg	200 mg 250 mg + 80 mg	4 x 50 mg 5 x 50 mg + 1 x 100 mg	365 365	1460 x 50 mg - 1825 x 50 mg + 365 x 100 mg
Darunavir FCT (600 mg)	≥ 15 kg 600 mg	600 mg	1 x 600 mg	365	365 x 600 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
+ Ritonavir FCT (100 mg)	+ 100 mg	+ 100 mg	+ 1 x 100 mg	365	+ 365 x 100 mg
Darunavir SUS (100 mg/ml) + Ritonavir POS (100 mg)	≥ 15 kg 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
Lopinavir/ ritonavir FCT (100/25 mg/ml)	BSA 0.50 to 0.9 200/50mg	400/100 mg	4 x 100/25 mg	365	1460 x 100/25 mg
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 GOS (10 mg/ml) CT (100 mg)	14 - < 20 kg 100 mg ≥ 20 kg 150 mg	200 mg – 300 mg	2 x 100 mg – 3 x 100 mg	365	730 x 100 mg – 1095 x 100 mg

b) Therapy-naive children with HIV-1 infection aged 6 to < 12 years

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					
Bictegravir/ emtricitabine/ tenofovir alafenamide	< 25 kg 30 mg/ 120 mg/15 mg	30 mg/ 120 mg/ 15 mg	1 x 30 mg/ 120 mg/ 15 mg	365	365 x 30 mg/ 120 mg/ 15 mg
Bictegravir/ emtricitabine/ tenofovir alafenamide	> 25 kg 50 mg/ 200 mg/ 25 mg	50 mg/ 200 mg/ 25 mg	1 x 50 mg/ 200 mg/ 25 mg	365	365 x 50 mg/ 200 mg/25 mg
Appropriate comparator therapy					
Base therapy (2 x NRTI: abacavir + lamivudine or abacavir + emtricitabine)					
Abacavir FCT (300 mg)	< 25 kg: 450 mg > 25 kg: 600 mg	450 mg – 600 mg	1.5 x 300 mg – 2 x 300 mg	365	547.5 x 300 mg – 730 x 300 mg
Emtricitabine OS (10 mg/ml)	24 - 33 kg 6 mg/kg 144 - 198 mg	150 mg – 200 mg	1 x 150 mg = 1 x 15 ml - 1 x 200 mg = 1 x 20.0 ml	365	365 x 15.0 ml – 365 x 20.0 ml
Emtricitabine HC (200 mg)	> 33 kg 200 mg	200 mg	1 x 200 mg	365	365 x 200 mg
Lamivudine FCT (150 mg; 300 mg)	< 25 kg 225 mg > 25 kg 300 mg	225 mg – 300 mg	1.5 x 150 mg – 2 x 150 mg or 1 x 300 mg	365	547.5 x 150 mg - 365 x 300 mg
Abacavir/ lamivudine FCT (600 mg/ 300 mg)	> 25 kg 600 mg/ 300 mg	600 mg/ 300 mg	1 x 600 mg/ 300 mg	365	365 x 600 mg/ 300 mg
3. Concomitant active ingredient for the above-mentioned base therapy					
Atazanavir HC (200 mg; 300 mg)	< 35 kg: 200 mg	200 mg	1 x 200 mg	365	365 x 200 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient / year	Average annual consumption by potency
+ ritonavir FCT (100 mg)	<u>> 35 kg</u> 300 mg + 100 mg	– 300 mg + 100 mg	– 1 x 300 mg + 1 x 100 mg	365	– 365 x 300 mg + 365 x 100 mg
Darunavir FCT (600 mg, 800 mg) + ritonavir FCT (100 mg)	<u>< 30 kg</u> 600 mg <u>> 40 kg</u> 800 mg + 100 mg	600 mg – 800 mg + 100 mg	1 x 600 mg – 1 x 800 mg + 1 x 100 mg	365 365	365 x 600 mg – 365 x 800 mg + 365 x 100 mg
Dolutegravir FCT (25 mg or 50 mg)	25 mg or 50 mg	50 mg	2 x 25 mg – 1 x 50 mg	365	730 x 25 mg – 365 x 50 mg

c) Therapy-naive adolescents with HIV-1 infection aged 12 to < 18 years

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					
Bictegravir/ emtricitabine/ tenofovir alafenamide	50 mg/ 200 mg/ 25 mg	50 mg/ 200 mg/ 25 mg	1 x 50 mg/ 200 mg/ 25 mg	365	365 x 50 mg/ 200 mg/25 mg
Appropriate comparator therapy					
Base therapy (2 x NRTI: tenofovir alafenamide + emtricitabine or abacavir + lamivudine or abacavir + emtricitabine)					
Abacavir FCT (300 mg)	600 mg	600 mg	2 x 300 mg	365	730 x 300 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient / year	Average annual consumption by potency
Abacavir/ lamivudine FCT (600 mg/ 300 mg)	600 mg/ 300 mg	600 mg/ 300 mg	1 x 600 mg/ 300 mg	365	365 x 600 mg/ 300 mg
Emtricitabine HC (200 mg)	200 mg	200 mg	1 x 200 mg	365	365 x 200 mg
Emtricitabine/ tenofovir alafenamide FCT (200mg/ 10 mg; 200 mg/ 25 mg)	200mg/ 10 mg or 200 mg/ 25 mg	200 mg/ 10 mg or 200 mg/ 25 mg	1 x 200 mg/ 10 mg or 1 x 200 mg/ 25 mg	365	365 x 200 mg/ 10 mg or 365 x 200 mg/ 25 mg
Lamivudine FCT (300 mg)	300 mg	300 mg	1 x 300 mg	365	365 x 300 mg
3. Concomitant active ingredient for the above-mentioned base therapy					
Atazanavir HC (300 mg) + ritonavir FCT (100 mg)	300 mg + 100 mg	300 mg + 100 mg	1 x 300 mg + 1 x 100 mg	365 365	365 x 300 mg + 365 x 100 mg
Darunavir FCT (800 mg) + ritonavir FCT (100 mg)	800 mg + 100 mg	800 mg + 100 mg	800 mg + 100 mg	365 365	800 mg + 100 mg
Dolutegravir FCT (25 mg or 50 mg)	25 mg or 50 mg	50 mg	2 x 25 mg or 1 x 50 mg	365	730 x 25 mg – 365 x 50 mg
Fixed combination of base therapy and concomitant active ingredient					
Emtricitabine/ tenofovir alafenamide + elvitegravir/ cobicistat	200 mg/ 10 mg/ 150 mg/ 150 mg	200 mg/ 10 mg/ 150 mg/ 150 mg	1 x 200 mg/ 10 mg/ 150 mg/ 150 mg	365	365 x 200 mg/ 10 mg/ 150 mg/ 150 mg

d) Therapy-experienced children and adolescents with HIV-1 infection aged 2 to < 18 years

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					
Bictegravir/ emtricitabine/ tenofovir alafenamide	30 mg/ 120 mg/ 15 mg	30 mg/ 120 mg/ 15 mg	1 x 30 mg/ 120 mg/ 15 mg	365	365 x 30 mg/ 120 mg/ 15 mg
Appropriate comparator therapy					
A patient-individual antiretroviral therapy with selection of approved active ingredients					
Abacavir FCT (300 mg)	300 mg	600 mg	2 x 300 mg	365	730 x 300 mg
Emtricitabine FCT (200 mg)	200 mg	200 mg	1 x 200 mg	365	365 x 25 mg
Emtricitabine/ tenofovir disoproxil FCT (200 mg/ 245 mg)	200 mg/ 245 mg	200 mg/ 245 mg	1 x 200 mg/ 245 mg	365	365 x 200 mg/ 245 mg
Nevirapine TAB (200 mg)	200 mg	400 mg	2 x 200 mg	365	730 x 200 mg
Enfuvirtide PSS (90 mg)	90 mg	180 mg	2 x 90 mg	365	730 x 90 mg

Costs:

Costs of the medicinal products:

a) Therapy-naive children with HIV-1 infection aged 2 to < 6 years

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					
Bictegravir/ emtricitabine/ tenofovir alafenamide 30 mg/ 120 mg/ 15 mg	30 FCT	€ 924.75	€ 2.00	€ 86.70	€ 836.05
Appropriate comparator therapy					
Abacavir 20 mg/ml	240 ml OS	€ 126.09	€ 2.00	€ 14.53	€ 109.56
Abacavir 300 mg	60 FCT	€ 485.84	€ 2.00	€ 64.18	€ 419.66
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
Darunavir 600 mg	180 FCT	€ 1,595.93	€ 2.00	€ 125.51	€ 1,468.42
Dolutegravir 5 mg	60 TOS	€ 145.37	€ 2.00	€ 5.30	€ 138.07
Emtricitabine 10 mg/ml	170 ml OS	€ 92.69	€ 2.00	€ 7.73	€ 82.96
Lamivudine 10 mg/ml	240 ml OS	€ 85.68	€ 2.00	€ 9.42	€ 74.26
Lamivudine 150 mg	80 FCT	€ 319.52	€ 2.00	€ 24.38	€ 293.14
Lopinavir/ ritonavir 80/20 mg/ml	5 x 60 ml OS	€ 827.97	€ 2.00	€ 103.36	€ 722.61
Lopinavir/ ritonavir 100/20 mg/ml	60 FCT	€ 233.43	€ 2.00	€ 28.11	€ 203.32
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
Ritonavir 100 mg	30 POS	€ 64.97	€ 2.00	€ 6.80	€ 56.17
Ritonavir 100 mg	90 FCT	€ 109.18	€ 2.00	€ 4.65	€ 102.53
Abbreviations: FCT = film-coated tablets; GOS = granules for oral suspension; HC = hard capsules; OS = oral solution; CT = chewable tablets; POS = powder for oral suspension; TOS = tablet for oral suspension; SUS = suspension					

b) Therapy-naive children with HIV-1 infection aged 6 to < 12 years

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					
Bictegravir/ emtricitabine/ tenofovir alafenamide 30 mg/ 120 mg/ 15 mg	30 FCT	€ 924.75	€ 2.00	€ 86.70	€ 836.05
Bictegravir/ emtricitabine/ tenofovir alafenamide 50 mg/ 200 mg/ 25 mg	90 FCT	€ 2,714.32	€ 2.00	€ 260.10	€ 2,452.22
Appropriate comparator therapy					
Abacavir 300 mg	60 FCT	€ 485.84	€ 2.00	€ 64.18	€ 419.66
Abacavir/ lamivudine 600/300 mg[7]	90 FCT	€ 200.19	€ 2.00	€ 14.94	€ 183.25
Atazanavir 200 mg	60 HC	€ 506.04	€ 2.00	€ 23.48	€ 480.56
Atazanavir 300 mg	30 HC	€ 389.63	€ 2.00	€ 17.96	€ 369.67
Darunavir 600 mg[9]	180 FCT	€ 1,595.93	€ 2.00	€ 125.51	€ 1,468.42
Darunavir 800 mg[9]	90 FCT	€ 1,020.02	€ 2.00	€ 79.79	€ 938.23
Dolutegravir 50 mg	90 FCT	€ 2,135.18	€ 2.00	€ 84.75	€ 2,048.43
Emtricitabine 10 mg/ml	170 ml OS	€ 92.69	€ 2.00	€ 7.73	€ 82.96
Emtricitabine 200 mg	30 HC	€ 302.71	€ 2.00	€ 27.66	€ 273.05
Lamivudine 150 mg	80 FCT	€ 319.52	€ 2.00	€ 24.38	€ 293.14
Lamivudine 300 mg	80 FCT	€ 587.91	€ 2.00	€ 45.61	€ 540.30
Ritonavir 100 mg	90 FCT	€ 109.18	€ 2.00	€ 4.65	€ 102.53
Abbreviations: FCT = film-coated tablets; HC = hard capsules; OS = oral solution					

[7] Fixed reimbursement rate

c) Therapy-naive adolescents with HIV-1 infection aged 12 to < 18 years

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					
Bictegravir/ emtricitabine/ tenofovir alafenamide 50 mg/ 200 mg/ 25 mg	90 FCT	€ 2,714.32	€ 2.00	€ 260.10	€ 2,452.22
Appropriate comparator therapy					
Abacavir 600 mg	60 FCT	€ 485.84	€ 2.00	€ 64.18	€ 419.66
Abacavir/ lamivudine 600/300 mg[9]	90 FCT	€ 200.19	€ 2.00	€ 14.94	€ 183.25
Atazanavir 300 mg	30 HC	€ 389.63	€ 2.00	€ 17.96	€ 369.67
Darunavir 800 mg[9]	90 FCT	€ 1,020.02	€ 2.00	€ 79.79	€ 938.23
Dolutegravir 50 mg	90 FCT	€ 2,135.18	€ 2.00	€ 84.75	€ 2,048.43
Emtricitabine 200 mg	30 HC	€ 302.71	€ 2.00	€ 27.66	€ 273.05
Emtricitabine/ tenofovir alafenamide 200 mg/10 mg	90 FCT	€ 197.21	€ 2.00	€ 14.71	€ 180.50
Emtricitabine/ tenofovir alafenamide 200 mg/25 mg	90 FCT	€ 200.66	€ 2.00	€ 14.98	€ 183.68
Emtricitabine/ tenofovir alafenamide + elvitegravir/ cobicistat 200mg/ 10mg/ 150 mg/ 150 mg	90 FCT	€ 2,714.32	€ 2.00	€ 260.10	€ 2,452.22
Lamivudine 300 mg	80 FCT	€ 587.91	€ 2.00	€ 45.61	€ 540.30
Ritonavir 100 mg	90 FCT	€ 109.18	€ 2.00	€ 4.65	€ 102.53
Abbreviations: FCT = film-coated tablets; HC = hard capsules					

d) Therapy-experienced children and adolescents with HIV-1 infection aged 2 to < 18 years

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					
Bictegravir/ emtricitabine/ tenofovir alafenamide 30 mg/ 120 mg/ 15 mg	30 FCT	€ 924.75	€ 2.00	€ 86.70	€ 836.05
Bictegravir/ emtricitabine/ tenofovir alafenamide 50 mg/ 200 mg/ 25 mg	90 FCT	€ 2,714.32	€ 2.00	€ 260.10	€ 2,452.22

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
Appropriate comparator therapy[8]					
Abacavir 300 mg	60 FCT	€ 485.84	€ 2.00	€ 64.18	€ 419.66
Emtricitabine 200 mg	30 HC	€ 302.71	€ 2.00	€ 27.66	€ 273.05
Nevirapine 200 mg	120 TAB	€ 240.19	€ 2.00	€ 10.86	€ 227.33
Enfuvirtide 90 mg	60 PSS	€ 2,350.00	€ 2.00	€ 231.05	€ 2,116.95
Emtricitabine/ tenofovir disoproxil 200 mg/ 245 mg[9]	90 FCT	€ 200.19	€ 2.00	€ 14.94	€ 183.25
Abbreviations: FCT = film-coated tablets; HC = hard capsules; PSS = powder and solvent for solution for injection; TAB = tablets					

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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 Bictegravir/ emtricitabine/ tenofovir alafenamide

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed

[8]Because of the different combination options in individual therapy, not all possible variants of combination therapies are presented and considered but the cost range from a cost-effective (emtricitabine/ tenofovir disoproxil + nevirapine) to a cost-intensive therapy (abacavir + emtricitabine + enfuvirtide) is specified as an example.

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 19 December 2022, the pharmaceutical company submitted a dossier for the benefit assessment of bictegravir/ 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 20 December 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 bictegravir/ emtricitabine/ tenofovir alafenamide.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 March 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 April 2023. The deadline for submitting statements was 24 April 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 and the oral hearing was discussed at the session of the subcommittee on 6 June 2023, and the proposed resolution was approved.

At its session on 15 June 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	26 April 2023	Information on statements received
Working group Section 35a	10 May 2023 31 May 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 June 2023	Concluding discussion of the draft resolution
Plenum	15 June 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 June 2023

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

Prof. Hecken