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 and Annex XIIa – Combinations with New Active Ingredients according to Section 35a SGB V
Dolutegravir/ abacavir/ lamivudine (new therapeutic indication:
HIV infection, ≥ 14 kg to < 12 years)

of 17 August 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 dolutegravir/ abacavir/ lamivudine (Triumeq) was listed for the first time on 1 October 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 20 February 2023, dolutegravir/ abacavir/ lamivudine 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 28 February 2023, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company, on the approval of a new therapeutic indication, has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8,

paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient dolutegravir/ abacavir/ lamivudine with the new therapeutic indication of HIV infection, ≥ 14 kg to < 12 years.

The G-BA came to a resolution on whether an additional benefit of dolutegravir/ abacavir/ lamivudine compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of dolutegravir/ abacavir/ lamivudine.

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 Dolutegravir/ abacavir/ lamivudine (Triumeq) according to the product information

Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected children weighing at least 14 kg to less than 25 kg.

Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children weighing at least 25 kg.

Before initiating treatment with abacavir-containing products, screening for carriage of the HLAB*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

Therapeutic indication of the resolution (resolution of 17 August 2023):

Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected children weighing at least 14 kg to < 12 years.

Before initiating treatment with abacavir-containing products, screening for carriage of the HLAB*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

a) Therapy naive children with HIV-1 infection ≥ 14 kg to < 6 years

Appropriate comparator therapy for dolutegravir/ abacavir/ lamivudine:

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

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

or dolutegravir + abacavir + emtricitabine

b) Therapy naive children with HIV-1 infection ≥ 14 kg from 6 to < 12 years

Appropriate comparator therapy for dolutegravir/ abacavir/ lamivudine:

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

- atazanavir + ritonavir or
- darunavir + ritonavir

or dolutegravir + abacavir + emtricitabine

c) Therapy experienced children with HIV-1 infection ≥ 14 kg to < 12 years

Appropriate comparator therapy for dolutegravir/ abacavir/ lamivudine:

- 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 dolutegravir/ abacavir/ lamivudine, the following active ingredients are generally approved for the treatment of HIV-1 infected children weighing at least 14 kg and aged < 12 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), didanosine

Non-nucleoside reverse transcriptase inhibitors (NNRTI): Nevirapine, efavirenz (from 3 months), etravirine (from 2 years)

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

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

Bictegravir/ emtricitabine/ tenofovir alafenamide (resolution of 15.06.2023)

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

Dolutegravir (resolution of 15 July 2021, amended by resolutions of 18 March 2022 and 6 October 2022)

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

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

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 infected children weighing at least 14 kg and aged < 12 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 HIV-1 infected children weighing at least 14 kg and aged < 12 years, 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.

Therapy naive HIV-1 infected children ≥ 14 kg to < 6 years

The S2K guideline recommends an ART regimen, which is composed of two NRTIs and a third component from either the PI, NNRTI or INI product class, as base therapy for therapy naive HIV-1 infected patients weighing at least 14 kg and aged < 6 years. 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 each with raltegravir or nevirapine or lopinavir/ ritonavir or atazanavir + ritonavir or darunavir + ritonavir as well as a combination therapy with dolutegravir

[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.

and abacavir and emtricitabine for therapy naive HIV-1 infected children weighing at least 14 kg and aged < 6 years must therefore considered equally appropriate.

Therapy naive children ≥ 14 kg from 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 ritonavir-boosted protein inhibitors atazanavir or darunavir 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 ritonavir-boosted protein inhibitors atazanavir or darunavir as well as the combination therapy with dolutegravir and abacavir and emtricitabine for therapy naive HIV-1 infected children weighing ≥ 14 kg and aged 6 to < 12 years must therefore be considered equally appropriate.

Therapy experienced children with HIV-1 infection ≥ 14 kg to < 12 years

When determining the appropriate comparator therapy for therapy experienced HIV-1 infected children and adolescents ≥ 14 kg to < 12 years, the evidence search showed that after one or more previous therapies, depending on the active ingredients/ product classes used and the reason for the change of therapy (e.g. therapy failure, side effects), patient-individual pharmacotherapy coordinated with the patient 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 regimen 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 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 dolutegravir/ abacavir/ lamivudine is assessed as follows:

For HIV-1 infected children ≥ 14 kg to < 12 years, an additional benefit is not proven.

Justification:

The pharmaceutical company does not present direct comparator data of dolutegravir/ abacavir/ lamivudine in the present therapeutic indication compared to the specific appropriate comparator therapy for both therapy naive and therapy experienced HIV-1 infected children ≥ 14 kg to < 12 years.

The single-arm, label-enabling IMPAACT 2019 study is unsuitable for the assessment of an additional benefit due to the lack of comparison with the appropriate comparator therapy.

Overall, no additional benefit can be derived for both therapy naive and therapy experienced HIV-1 infected children weighing ≥ 14 kg and aged < 12 years compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the combination of active ingredients dolutegravir/ abacavir/ lamivudine (Triumeq).

Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected children weighing at least 14 kg and aged < 12 years.

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

a) <u>Therapy naive children with HIV-1 infection ≥ 14 kg to < 6 years</u>

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

The single-arm, label-enabling IMPAACT 2019 study is unsuitable for the assessment of an additional benefit due to the lack of comparison with the appropriate comparator therapy.

Overall, no additional benefit can be derived for therapy naive HIV-1 infected children weighing ≥ 14 kg and aged < 6 years compared to the appropriate comparator therapy.

b) Therapy naive children with HIV-1 infection ≥ 14 kg from 6 to < 12 years

The G-BA determined abacavir with lamivudine or abacavir with emtricitabine, each in combination with atazanavir + ritonavir or darunavir + ritonavir, as well as the combination therapy with dolutegravir and abacavir and emtricitabine as the appropriate comparator therapy for dolutegravir/ abacavir/ lamivudine.

The single-arm, label-enabling IMPAACT 2019 study is unsuitable for the assessment of an additional benefit due to the lack of comparison with the appropriate comparator therapy.

Overall, no additional benefit can be derived for therapy naive HIV-1 infected children weighing ≥ 14 kg and aged 6 to < 12 years compared to the appropriate comparator therapy.

c) Therapy experienced children with HIV-1 infection ≥ 14 kg to < 12 years

The G-BA determined an appropriate comparator therapy for dolutegravir/ abacavir/ lamivudine 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.

The single-arm, label-enabling IMPAACT 2019 study is unsuitable for the assessment of an additional benefit due to the lack of comparison with the appropriate comparator therapy.

Overall, no additional benefit can be derived for therapy experienced HIV-1 infected children weighing ≥ 14 kg and aged < 12 years compared to the appropriate comparator therapy.

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

HIV-1 infected children weighing ≥ 14 kg aged < 12 years

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 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@RKI2.0[5] database is 105 children aged ≥ 2 to < 12 years who were infected with HIV-1 in 2022. The pharmaceutical company assumes 7.2%[6] as the percentage of carriers of the HLA-B*5701 allele in Germany. This results in 97 patients who do not carry the HLA-B*5701 allele. Based on data from the Federal Health Reporting, 87.8% of the

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

[6] Orkin C, Wang J, Bergin C et al. An epidemiologic study to determine the prevalence of HLA-B*5701 allele among HIV-positive patients in Europe. Pharmacogenetics and Genomics 2010; 20 (05): 307-314

population has statutory health insurance. This results in a total of 86 patients in the SHI target population.

However, the pharmaceutical company does not provide information on therapy naive children ≥ 14 kg to < 6 years, 6 to < 12 years and therapy experienced children ≥ 14 kg to < 12 years.

Most recently, the number of children with HIV-1 from the age group under consideration here was quantified in the bictegravir/ emtricitabine/ tenofovir alafenamide trial (resolution of 15.06.2023). The identical data source was used as a starting point for the calculation (SurvStat@RKI2.0 database[5]). Assuming that only the cases diagnosed in the most recent year have no prior treatment, the following patient numbers result in the SHI target population for the respective age categories, taking into account the calculation basis from the procedure for bictegravir/ emtricitabine/ tenofovir alafenamide for therapy naive children: ≥ 14 kg up to < 6 years, approx. 4 patients, ≥ 14 kg from 6 to < 12 years approx. 15 patients. For therapy experienced children in the SHI target population ≥ 14 kg to < 12 years, this results in approx. 67 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 Triumeq (active ingredient: dolutegravir/ abacavir/ lamivudine) at the following publicly accessible link (last access: 16 May 2023):

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

Treatment with dolutegravir/ abacavir/ lamivudine 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 June 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. 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 m^2 (calculation according to Du Bois 1916) results for children aged 2 to < 6 years.

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 ≥ 14 kg 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				
Dolutegravir/ abacavir/ lamivudine	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Lopinavir/ ritonavir or raltegravir or nevirapine or atazanavir + ritonavir or darunavir + ritonavir, each 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
Concomitant active ingredient for the above-mentioned base therapy				
Atazanavir + ritonavir	Continuously, 1 x daily Continuously, 1 x daily	365 365	1 1	365 365
Darunavir + ritonavir	Continuously, 1 x daily Continuously, 1 x daily	365 365	1 1	365 365
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
Dolutegravir	Continuously, 1 x daily	365	1	365

b) Therapy naive children with HIV-1 infection ≥ 14 kg from 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				
Dolutegravir/ abacavir/ lamivudine	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Atazanavir + ritonavir or darunavir + ritonavir, each 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
Abacavir/ lamivudine	Continuously, 1 x daily	365	1	365
Concomitant active ingredient for the above-mentioned base therapy				
Atazanavir + ritonavir	Continuously, 1 x daily Continuously, 1 x daily	365 365	1 1	365 365
Darunavir + ritonavir	Continuously, 1 x daily Continuously, 1 x daily	365 365	1 1	365 365
Dolutegravir	Continuously, 1 x daily	365	1	365

c) Therapy experienced children with HIV-1 infection ≥ 14 kg to < 12 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 (abacavir/ lamivudine + nevirapine) to a cost-intensive therapy (abacavir + emtricitabine + maraviroc) 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				
Dolutegravir/ abacavir/ lamivudine	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
Abacavir/ lamivudine	Continuously 1 x daily	365	1	365
Nevirapine	Continuously, 2 x daily	365	1	365
Emtricitabine	Continuously, 1 x daily	365	1	365
Maraviroc	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 ≥ 14 kg 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					
Dolutegravir/ abacavir/ lamivudine	25|300| 150 mg - 30|360| 180 mg	25|300| 150 mg - 30|360| 180 mg	5 – 6 x 5|60|30 mg	365	1,825 – 2,190 x 5|60|30 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: 300 - 450 mg	300 – 450 mg	1 – 1.5 x 300 mg	365	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
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	1,460 x 50 mg - 1,825 x 50 mg + 365 x 100 mg
Darunavir FCT (600 mg) + Ritonavir FCT (100 mg)	≥ 15 kg 600 mg + 100 mg	600 mg + 100 mg	1 x 600 mg + 1 x 100 mg	365 365	365 x 600 mg + 365 x 100 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
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
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	1,460 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 GSE (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 - 1,095 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	1,825 x 5 mg - 2,190 x 5 mg

b) Therapy naive children with HIV-1 infection ≥ 14 kg from 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					
Dolutegravir/ abacavir/ lamivudine	30|360| 180 mg	30|360| 180 mg	6 x 5|60|30 mg	365	2,190 x 5|60|30 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
Dolutegravir/ abacavir/ lamivudine	50| 600|300 mg	50| 600|300 mg	1 x 50| 600|300 mg	365	365 x 50|600|300 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) + ritonavir FCT (100 mg)	< 35 kg: 200 mg > 35 kg 300 mg + 100 mg	200 mg - 300 mg + 100 mg	1 x 200 mg - 1 x 300 mg + 1 x 100 mg	365 365	365 x 200 mg - 365 x 300 mg + 365 x 100 mg
Darunavir FCT (600 mg, 800 mg) + ritonavir FCT (100 mg)	< 30 kg 600 mg > 40 kg 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 (50 mg)	50 mg	50 mg	1 x 50 mg	365	365 x 50 mg

c) Therapy experienced children with HIV-1 infection ≥ 14 kg 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					
Dolutegravir/ abacavir/ lamivudine	30|360| 180 mg	30|360| 180 mg	6 x 5|60|30 mg	365	2,190 x 5|60|30 mg
Dolutegravir/ abacavir/ lamivudine	50|600| 300 mg	50|600| 300 mg	1 x 50| 600|300 mg	365	365 x 50|600|300 mg
Appropriate comparator therapy					
A patient-individual antiretroviral therapy with selection of approved active ingredients					
Abacavir	300 mg	600 mg	2 x 300 mg	365	730 x 300 mg
abacavir/ lamivudine	600/ 300 mg	600/ 300 mg	1 x 600/300 mg	365	365 x 600/300 mg
Nevirapine	200 mg	400 mg	2 x 200 mg	365	730 x 200 mg
Emtricitabine	200 mg	200 mg	1 x 200 mg	365	365 x 200 mg
Maraviroc	300 mg	600 mg	2 x 300 mg	365.0	730 x 300 mg

Costs:

Costs of the medicinal products:

a) Therapy naive children with HIV-1 infection ≥ 14 kg 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					
Dolutegravir/ abacavir/ lamivudine 5|60|30 mg	90 TOS	€ 504.37	€ 2.00	€ 19.50	€ 482.87
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	€ 60.06	€ 423.78
Atazanavir 50 mg	30 POS	€ 174.44	€ 2.00	€ 15.49	€ 156.95
Darunavir 100 mg/ml	200 ml SUS	€ 827.26	€ 2.00	€ 77.45	€ 747.81
Darunavir 600 mg[7]	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[7]	80 FCT	€ 319.52	€ 2.00	€ 24.38	€ 293.14
Lopinavir/ ritonavir 80/20 mg/ml	5 x 60 ml OS	€ 884.31	€ 2.00	€ 110.48	€ 771.83
Lopinavir/ ritonavir 100/25 mg	60 FCT	€ 248.76	€ 2.00	€ 30.05	€ 216.71
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	€ 68.66	€ 2.00	€ 7.26	€ 59.40
Ritonavir 100 mg	90 FCT	€ 108.58	€ 2.00	€ 4.62	€ 101.96
Abbreviations: FCT = film-coated tablets; GOS = granules for oral suspension; OS = oral solution; CT = chewable tablets; POS = powder for oral suspension; SUS = suspension; TOS = tablet for oral suspension					

[7] Fixed reimbursement rate

b) Therapy naive children with HIV-1 infection ≥ 14 kg from 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					
Dolutegravir/ abacavir/ lamivudine 5|60|30 mg	90 TOS	€ 504.37	€ 2.00	€ 19.50	€ 482.87
Dolutegravir/ abacavir/ Lamivudine 50|600|300 mg	90 TOS	€ 2,925.76	€ 2.00	€ 117.00	€ 2,806.76
Appropriate comparator therapy					
Abacavir 300 mg	60 FCT	€ 485.84	€ 2.00	€ 60.06	€ 423.78
Abacavir/ lamivudine 600/300 mg[8]	90 FCT	€ 200.19	€ 2.00	€ 14.94	€ 183.25
Atazanavir 200 mg	60 HC	€ 506.02	€ 2.00	€ 23.48	€ 480.54
Atazanavir 300 mg	90 HC	€ 1,124.42	€ 2.00	€ 52.83	€ 1,069.59
Darunavir 600 mg[8]	180 FCT	€ 1,595.93	€ 2.00	€ 125.51	€ 1,468.42
Darunavir 800 mg[8]	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[8]	80 FCT	€ 319.52	€ 2.00	€ 24.38	€ 293.14
Lamivudine 300 mg[8]	80 FCT	€ 587.91	€ 2.00	€ 45.61	€ 540.30
Ritonavir 100 mg	90 FCT	€ 108.58	€ 2.00	€ 4.62	€ 101.96
Abbreviations: FCT = film-coated tablets; HC = hard capsules; OS = oral solution, TOS = tablets for oral suspension					

c) Therapy experienced children with HIV-1 infection ≥ 14 kg 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					
Dolutegravir/ abacavir/ lamivudine 5|60|30 mg	90 TOS	€ 504.37	€ 2.00	€ 19.50	€ 482.87
Dolutegravir/ abacavir/ Lamivudine 50|600|300 mg	90 TOS	€ 2,925.76	€ 2.00	€ 117.00	€ 2,806.76

[8] Fixed reimbursement rate

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[9]					
Abacavir 300 mg	60 FCT	€ 485.84	€ 2.00	€ 60.06	€ 423.78
Abacavir/ lamivudine 600/300 mg[8]	90 FCT	€ 200.19	€ 2.00	€ 14.94	€ 183.25
Nevirapine 200 mg	120 TAB	€ 240.19	€ 2.00	€ 10.86	€ 227.33
Emtricitabine 200 mg	30 HC	€ 302.71	€ 2.00	€ 27.66	€ 273.05
Maraviroc 300 mg	60 FCT	€ 1,073.30	€ 2.00	€ 100.80	€ 970.50
Abbreviations: FCT = film-coated tablets; HC = hard capsules; PSI = powder and solvent for solution for injection; TAB = tablets; TOS = tablet for oral 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.

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

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 Dolutegravir/ abacavir/ lamivudine

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 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 designated medicinal products are each an active ingredient that can be used in combination therapy with the assessed medicinal product on the basis of an open-label combination. This results from the fact that, on the one hand, the product information for the assessed medicinal product does not contain any information on combination therapies and, on the other, this product information does not contain any information that regularly contradicts a combination therapy with the assessed medicinal product.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the specifications in the product information for the designated medicinal products, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive, which serves search purposes.

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 26 April 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 February 2023, the pharmaceutical company submitted a dossier for the benefit assessment of dolutegravir/ abacavir/ lamivudine to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 1 March 2023 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 dolutegravir/ abacavir/ lamivudine.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 May 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 June 2023. The deadline for submitting written statements was 22 June 2023.

The oral hearing was held on 10 July 2023.

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 8 August 2023, and the proposed resolution was approved.

At its session on 17 August 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 April 2022	Determination of the appropriate comparator therapy
Working group Section 35a	4 July 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 July 2023	Conduct of the oral hearing
Working group Section 35a	18 July 2023 1 August 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	8 August 2023	Concluding discussion of the draft resolution
Plenum	17 August 2023	Resolution on the amendment of Annex XII and the amendment of Annex XIIa Pharmaceuticals Directive

Berlin, 17 August 2023

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

Prof. Hecken