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 Doravirine/ Lamivudine/ Tenofovir Disoproxil (new therapeutic indication: HIV infection, 12 to < 18 years)

of 20 October 2022

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 doravirine/ lamivudine/ tenofovir disoproxil (Delstrigo) was listed for the first time on 15 January 2019 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 28 March 2022, Delstrigo 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, p. 7).

On 22 April 2022, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time 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 combination doravirine/ lamivudine/ tenofovir disoproxil with the new therapeutic indication (HIV infection, adolescents aged 12 to < 18 years).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 August 2022 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of doravirine/ lamivudine/ tenofovir disoproxil 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 doravirine/ lamivudine/ tenofovir disoproxil.

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 Doravirine/ Lamivudine/ Tenofovir Disoproxil (Delstrigo) according to the product information

Delstrigo is also indicated for the treatment of adolescents aged 12 years and older weighing at least 35 kg who are infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil.

Therapeutic indication of the resolution (resolution of 20 October 2022):

Delstrigo is indicated for the treatment of adolescents aged 12 to < 18 years weighing at least 35 kg who are infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Therapy experienced adolescents with HIV-1 infection aged 12 to < 18 years without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir disoproxil

Appropriate comparator therapy for doravirine/ lamivudine/ tenofovir disoproxil:

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.

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

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. Active ingredients generally approved for the treatment of infection with HIV in adolescents aged 12 to < 18 years are:

Protease inhibitors (PI): Lopinavir, atazanavir, ritonavir, tipranavir, darunavir, fosamprenavir

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

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

Integrase inhibitors (INI): Raltegravir, dolutegravir, elvitegravir

Other antivirals: Maraviroc (entry inhibitor), enfuvirtide (entry inhibitor)

Other therapeutic agents: Cobicistat (pharmacokinetic amplifier)

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 adolescents aged 12 to < 18 years:

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)*
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 adolescents aged 12 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 adolescents aged 12 to < 18 years with HIV-1, only the German-Austrian S2k guideline describes the resistance situation in the German healthcare context. In addition, the written statements of the participating scientific-medical societies and the statements of the clinical experts as part of the written statement procedure for the individual age categories are in agreement with the recommendations of the S2k guideline. The German-Austrian S2k guideline is therefore used to determine the appropriate comparator therapy.

When determining the appropriate comparator therapy for therapy experienced adolescents, 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 is recommended. The naming of a defined combination of active ingredients in the sense of a therapy standard after therapy failure is not possible 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.

The pivotal use of the medicinal products, 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.

[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.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of doravirine/ lamivudine/ tenofovir disoproxil is assessed as follows:

For therapy experienced adolescents with HIV-1 infection aged 12 to < 18 years without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir disoproxil, an additional benefit of doravirine/ lamivudine/ tenofovir disoproxil compared with the appropriate comparator therapy is not proven.

Justification:

The pharmaceutical company does not present direct comparator data of doravirine/ lamivudine/ tenofovir disoproxil versus the specific appropriate comparator therapy for patients aged 12 to under 18 years with HIV infection.

In addition, the pharmaceutical company presents the ongoing, single-arm, pivotal study IMPACT 2014, which was conducted in two cohorts.

In cohort 1, 9 virologically suppressed adolescents received doravirine in addition to their antiretroviral therapy. Pharmacokinetics and safety were studied until day 14. In cohort 2, 43 pretreated and 2 therapy naive adolescents received doravirine in fixed combination with lamivudine and tenofovir disoproxil once daily for 96 weeks. The endpoints were adverse events at week 24, 48 and 96.

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 IMPAACT 2014 study, no additional benefit compared to the appropriate comparator therapy can be derived for therapy experienced adolescents with HIV-1 infection aged 12 to < 18 years without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir disoproxil.

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 doravirine/ lamivudine/ tenofovir disoproxil (Delstrigo®).

Doravirine/ lamivudine/ tenofovir disoproxil is indicated for the treatment of adolescents aged 12 to < 18 years weighing at least 35 kg who are infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil.

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

The pharmaceutical company submits the pivotal, single-arm study IMPAACT 2014, in addition. This study is not relevant for the present benefit assessment, as no data are available for an assessment of doravirine in comparison with the appropriate comparator therapy.

Overall, the pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of doravirine/ lamivudine/ tenofovir disoproxil

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

Based on the information on patient numbers from the Robert Koch Institute, the pharmaceutical company assumes 146 - 154 patients with HIV-1 infection aged 12 to < 18 years in Germany. The pharmaceutical company delimits those patients in whom a change of therapy is carried out (37.7 - 40.3%), in whom a change of therapy is carried out due to toxicity (30.9 - 40.3%) and who show resistance to NRTIs (5.3 - 12.9%) or NNRTIs (3.9%). Assuming that approx. 88.1% of the German resident population has statutory health insurance, according to the pharmaceutical company approx. 11 to 21 pretreated adolescents aged 12 to < 18 years are eligible for the administration of doravirine/ lamivudine/ tenofovir disoproxil.

The number of patients in the SHI target population stated by the pharmaceutical company is to be regarded as uncertain overall, in particular due to the non-consideration of mortality, uncertainties in the percentage of patients with a change of therapy, an underestimation of the percentage of pretreated patients and an overestimation of the determined percentage values for the resistance situation.

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 Delstrigo (active ingredient: doravirine/ lamivudine/ tenofovir disoproxil) at the following publicly accessible link (last access: 1 October 2022):

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

Treatment with doravirine/ lamivudine/ tenofovir disoproxil should only be initiated and monitored by specialists who are experienced in the treatment of patients with HIV-1.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 October 2022).

For the appropriate comparator therapy of adolescents with previous antiretroviral treatment, the range of treatment costs incurred depending on the individual choice of therapy is shown. Because of the different combination possibilities in individual therapy, not all possible variants of combination therapies are presented and considered but a cost-effective (nevirapine + emtricitabine/ tenofovir disoproxil) and a cost-intensive therapy (enfuvirtide + abacavir + emtricitabine) as an example.

According to the current German guideline[5], different alternatives ("backbone" and concomitant active ingredient) are recommended; these were taken into account for the cost representation.

[5] German-Austrian guidelines on antiretroviral therapy of HIV infection (consented version 2017)

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Doravirine/ lamivudine/ tenofovir disoproxil	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Nevirapine + emtricitabine/ tenofovir disoproxil				
Nevirapine	continuously, 2 x daily	365	1	365
Emtricitabine/ tenofovir disoproxil	continuously, 1 x daily	365	1	365
Enfuvirtide + abacavir + emtricitabine				
Enfuvirtide	continuously, 2 x daily	365	1	365
Abacavir	continuously, 2 x daily	365	1	365
Emtricitabine	continuously, 1 x daily	365	1	365

Consumption:

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.

The average body measurements were applied for dosages depending on body weight (bw) or body surface area (BSA) (average body height of a child aged above 12 years: 1.56 m, average body weight 47.1 kg; average body height of an adolescent aged between 17 and under 18 years: 1.74 m; average body weight 67.0 kg).[6]

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

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					
Doravirine/ lamivudine/ tenofovir disoproxil	100 mg/ 300 mg/ 245 mg	100 mg/ 300 mg/ 245 mg	1 x 100 mg/ 300 mg/ 245 mg	365	365 x 100 mg/ 300 mg/ 245 mg
Appropriate comparator therapy					
Nevirapine + emtricitabine/ tenofovir disoproxil					
Nevirapine	200 mg	400 mg	2 x 200 mg	365	730 x 200 mg
Emtricitabine/ tenofovir disoproxil	200 mg/ 245 mg	200 mg/ 245 mg	1 x 200 mg/ 245 mg	365	365 x 200 mg/ 245 mg
Enfuvirtide + abacavir + emtricitabine					
Enfuvirtide	90 mg	180 mg	2 x 90 mg	365	730 x 90 mg
Abacavir	300 mg	600 mg	2 x 300 mg	365	730 x 300 mg
Emtricitabine	200 mg	200 mg	1 x 200 mg	365	365 x 25 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Doravirine 100 mg/ lamivudine 300 mg/ tenofovir disoproxil 245 mg	90 FCT	€ 2,433.88	€ 1.77	€ 135.71	€ 2,296.40
Appropriate comparator therapy					
Abacavir 300 mg	180 FCT	€ 1,107.33	€ 1.77	€ 52.01	€ 1,053.55
Emtricitabine 200 mg	30 HC	€ 302.71	€ 1.77	€ 16.14	€ 284.80
Emtricitabine 200 mg/ tenofovir disoproxil 245 mg[7]	90 FCT	€ 200.19	€ 1.77	€ 14.94	€ 183.48

[7] 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
Enfuvirtide 90 mg	60 PSI	€ 2,350.00	€ 1.77	€ 137.91	€ 2,210.32
Nevirapine 200 mg	120 TAB	€ 267.21	€ 1.77	€ 12.73	€ 252.71
Abbreviations: FCT = film-coated tablets, HC = hard capsules, PSI = powder and solvent for solution for injection, TAB = tablets					

LAUER-TAXE® last revised: 1 October 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs 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 22 April 2022, the pharmaceutical company submitted a dossier for the benefit assessment of doravirine/ lamivudine/ tenofovir disoproxil to the G- BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 April 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 doravirine/ lamivudine/ tenofovir disoproxil.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 July 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 August 2022. The deadline for submitting written statements was 22 August 2022.

The oral hearing was held on 5 September 2022.

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 05 September 2022, and the proposed resolution was approved.

At its session on 20 October 2022, 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	31 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 September 2022	Conduct of the oral hearing,
Working group Section 35a	14 September 2022 5 October 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	11 October 2022	Concluding discussion of the draft resolution
Plenum	20 October 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 October 2022

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

Prof. Hecken