Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V

Dolutegravir (New Therapeutic Indication: HIV infection, children ≥ 4 weeks to < 6 years)

of 15 July 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA

electronically, including all clinical 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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient dolutegravir (Tivicay) was listed for the first time on 15 February 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 11 January 2021, dolutegravir 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 December 2008, p. 7).

On 29 January 2021, 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 with the new therapeutic indication (HIV infection, children ≥ 4 weeks to < 6 years).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 3 May 2021 on the G-BA website at (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of dolutegravir 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.

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 (tivicay) in accordance with the product information

Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children of at least 4 weeks of age or older and weighing at least 3 kg.

Therapeutic indication of the resolution (resolution of 15.07.2021):

Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) paediatric patients aged 4 weeks to below 6 years and weighing at least 3 kg.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) <u>Therapy naïve children with HIV-1 infection aged ≥ 4 weeks to < 6 years</u>

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

- Lopinavir/ritonavir or
- raltegravir or
- Nevirapine

b) <u>Therapy-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years</u>

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

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

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 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 Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. The following active ingredients are generally approved for the treatment of HIV-1 infection in children aged 4 weeks to < 6 years (taking into account any approved age restrictions):

Protease inhibitors (PI): lopinavir/ritonavir (from 2 weeks), atazanavir (from 3 months), ritonavir (from 2 years), tipranavir (from 2 years), darunavir (from 3 years), etravirine (from 2 years)

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

Non-nucleoside reverse transcriptase inhibitors (NNRTI): nevirapine, efavirenz (from 3 months)

Integrase inhibitors (INI): Raltegravir

Other antivirals: maraviroc (entry inhibitor; from 2 years)

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

on 3. In the present therapeutic indication, there are no resolutions and guidelines of the G-BA.

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication.

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

Both guidelines recommend an ART regimen as base therapy for therapy naïve patients, 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 WHO and German-Austrian S2k guidelines recommend the active ingredients raltegravir, nevirapine, and lopinavir boosted with ritonavir. The active ingredients darunavir and atazanavir boosted with ritonavir are only recommended by the German-Austrian S2k guideline, reflecting the German health care context but having a lower evidence level than the WHO guideline in terms of methodological assessment. For this reason, these two active ingredients as well as the active ingredient efavirenz, are not considered appropriate in this therapeutic indication due to its spectrum of side effects.

The following active ingredients mentioned in 1. are not recommended by the guidelines: atazanavir, tipranavir, zidovudine, tenofovir disoproxil, maraviroc.

Overall, combination therapy of abacavir and lamivudine or abacavir and emtricitabine with raltegravir, nevirapine and lopinavir/ritonavir is therefore considered to be equally appropriate.

When determining the appropriate comparator therapy for therapy experienced children, the evidence search showed that after one or more previous therapies,

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[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. [Accessed: 16/6/2020]. URL: https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1.

[3] **World Health Organization (WHO).** Update of recommendations on first- and second-line anti-retroviral regimens: policy brief [online]. Geneva (SUI): WHO Press; 2019. [Accessed: 16/6/2020]. URL: https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1.

[4] **German-Austrian guidelines** on anti-retroviral therapy of HIV infection in children and adolescents [online]. AWMF register number 048-011. Berlin (GER): Association of the Scientific Medical Societies (AWMF); 2019. [Accessed: 16/6/2020]. URL: https://www.awmf.org/uploads/tx_szleitlinien/048-011l_S2k_antiretrovirale_Therapie_der_HIV_Infektion_bei_Kindern_Jugendlichen_2019-12.pdf.

depending on the active ingredient(s)/medicinal 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 scheme depending on the previous therapy. In principle, all possible combinations of active ingredients can therefore be regarded as appropriate.

In both therapy naïve and therapy-experienced children with HIV-1 infection, the use of the medicinal products in compliance with 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.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of dolutegravir is assessed as follows:

a) Therapy naïve children with HIV-1 infection aged ≥ 4 weeks to < 6 years

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of dolutegravir for the treatment of HIV infections in children from 4 weeks to < 6 years of age, the marketing authorisation justifying single-arm studies IMPAACT P1093 and ODYSSEY WB-PK1/2 were submitted by the pharmaceutical company.

The IMPAACT P1093 study is a 1-arm, multicenter, open-label trial of dolutegravir in HIV-1 infected children and adolescents aged ≥ 4 weeks to < 18 years with a bodyweight of at least 3 kg. The study included both therapy naïve patients and pretreated patients with anti-retroviral therapy (ART).

In his dossier, the pharmaceutical company presents data on a subpopulation of 51 children in whom the age (≥ 4 weeks to < 6 years) and the dosage form used of dolutegravir (tablet for oral suspension) correspond to the present therapeutic indication. 86.3% of children were pretreated with ART.

In the IMPAACT P1093 study, dolutegravir was administered in combination with an optimised anti-retroviral background therapy according to the product information requirements according to body weight and age. The dose of dolutegravir used in the IMPAACT P1093 study for children older than 6 months and weighing less than 6 kg differs from that specified in the product information.

The primary endpoint of the IMPAACT P1093 study was adverse events (AEs) through week 24. Secondary patient-relevant endpoints were AEs up to week 48. The study is still ongoing and the treatment duration is 48 weeks.

The ODYSSEY WB-PK1/2 study is a pharmacokinetic substudy of the RCT ODYSSEY. The ODYSSEY WB-PK1/2 study included therapy naïve as well as ART-pretreated patients from the dolutegravir arm of the ODYSSEY study with a bodyweight of ≥ 3 kg to < 40 kg. The proportion of therapy-naïve patients is 81, 3%.

The primary endpoint of the ODYSSEY WB-PK1/2 study was pharmacokinetics. Patient-relevant secondary endpoints were AEs. The duration of treatment is 96 weeks.

For the optimised anti-retroviral background therapy used in the IMPAACT P1093 and ODYSSEY WB-PK1/2 studies, the dossier only contains information on the product classes, active ingredients used, and resistance at the start of the study were not provided.

The single-arm studies IMPAACT P1093 and ODYSSEY WB-PK1/2 are not relevant for the present benefit assessment, as no data are available for an assessment of dolutegravir compared with the appropriate comparator therapy.

Even though the marketing authorisation for children ≥ 4 weeks to < 6 years of age was granted by the EMA based on extrapolation of pharmacokinetic/dynamic data, no transfer of additional benefit from adults to children can be made in the present benefit assessment procedure, as the conditions are not met that would justify recognition of additional benefit for children ≥ 4 weeks to < 6 years of age based on adult results.

The appropriate comparator therapy for adults (efavirenz in combination with abacavir plus lamivudine) defined by the G-BA differs from the appropriate comparator therapy for children aged ≥ 4 weeks to < 6 years (abacavir with lamivudine or abacavir with emtricitabine, in each case in combination with lopinavir/ritonavir or raltegravir or nevirapine), which means that a fundamental criterion for an evidence transfer in the benefit assessment is not met. Consequently, a transfer of the additional benefit of dolutegravir of therapy naïve adults to therapy naïvechildren is not justified on the basis of the studies SINGLE and SPRING-1 on which the benefit assessment for adults is based. In addition, in the SPRING-1 study only, a small proportion of adult patients were treated with the pediatric base therapy (abacavir + lamivudine) (N= 17 in the dolutegravir arm and N= 16 in the efavirenz arm).

The recognition of an additional benefit for children on the basis of results in adults is therefore not possible.

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 dolutegravir compared with the appropriate comparator therapy.

An additional benefit of dolutegravir compared to the appropriate comparator therapy is therefore not proven.

b) <u>Therapy-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years</u>

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of dolutegravir for the treatment of HIV infections in children from 4 weeks to < 6 years of age, the marketing authorisation justifying single-arm studies IMPAACT P1093 and ODYSSEY WB-PK1/2 were submitted by the pharmaceutical company.

The IMPAACT P1093 study is a 1-arm, multicenter, open-label trial of dolutegravir in HIV-1 infected children and adolescents aged ≥ 4 weeks to < 18 years with a bodyweight of at least 3 kg. The study included both therapy naïve patients and pretreated patients with anti-retroviral therapy (ART).

In his dossier, the pharmaceutical company presents data on a subpopulation of 51 children in whom the age (≥ 4 weeks to < 6 years) and the dosage form used of dolutegravir (tablet for oral suspension) correspond to the present therapeutic indication. 86.3% of children were pretreated with ART.

In the IMPAACT P1093 study, dolutegravir was administered in combination with an optimised anti-retroviral background therapy in accordance with the requirements in the product information of the technical information according to body weight and age. The dose of dolutegravir used in the IMPAACT P1093 study for children older than 6 months and weighing less than 6 kg differs from that specified in the product information.

The primary endpoint of the IMPAACT P1093 study was adverse events (AEs) through week 24. Secondary patient-relevant endpoints were AEs up to week 48. The study is still ongoing, and the treatment duration is 48 weeks.

The ODYSSEY WB-PK1/2 study is a pharmacokinetic substudy of the RCT ODYSSEY. The ODYSSEY WB-PK1/2 study included therapy naïve as well as ART-pretreated patients from the dolutegravir arm of the ODYSSEY study with a bodyweight of ≥ 3 kg to < 40 kg.

The primary endpoint of the ODYSSEY WB-PK1/2 study was pharmacokinetics. Patient-relevant secondary endpoints were AEs. The duration of treatment is 96 weeks.

For the optimised anti-retroviral background therapy used in the IMPAACT P1093 and ODYSSEY WB-PK1/2 studies, the dossier only contains information on the product classes, active ingredients used and resistance at the start of the study were not provided.

The single-arm studies IMPAACT P1093 and ODYSSEY WB-PK1/2 are not relevant for the present benefit assessment, as no data are available for an assessment of dolutegravir compared with the appropriate comparator therapy.

Even though the marketing authorisation for children ≥ 4 weeks to < 6 years of age was granted by the EMA based on extrapolation of pharmacokinetic/dynamic data, no transfer of additional benefit from adults to children can be made in the present benefit assessment procedure, as the conditions are not met that would justify recognition of additional benefit for children ≥ 4 weeks to < 6 years of age based on adult results.

The appropriate comparator therapy defined by the G-BA for therapy-experienced adults for whom treatment with an integrase inhibitor is the first therapy option (raltegravir in combination with an individual backbone therapy depending on the previous therapy(ies) and taking into account the reason for the change in therapy, in particular, treatment failure due to virological failure and any associated development of resistance or due to side effects)

differs from the appropriate comparator therapy for children aged ≥ 4 weeks to < 6 years (a patient-individual anti-retroviral therapy with a choice of approved agents; taking into account the previous therapy(ies) and the reason for the change in therapy, in particular, therapy failure due to virological failure and any associated development of resistance or due to side effects), which means that a fundamental criterion for a transfer of evidence in the benefit assessment is not met.

A transfer of the additional benefit of dolutegravir of therapy-experienced adults, for whom treatment with an integrase inhibitor is the first therapy option, to therapy-experienced children is not justified based on the SAILING study on which the benefit assessment for adults is based, in particular, because the study populations of the adult and paediatric studies are not sufficiently reliably comparable (e.g. concerning the initial viral load).

In the present benefit assessment procedure, it is also not possible to transfer an additional benefit for therapy-experienced adults, for whom treatment with an integrase inhibitor is a lower-ranking therapy option, because the benefit assessment procedure for this patient population (resolution date: 7 August 2014), no additional benefit was identified because no assessable data were available.

The recognition of an additional benefit for children based on results in adults is therefore not possible.

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 dolutegravir compared with the appropriate comparator therapy.

An additional benefit of dolutegravir compared to the appropriate comparator therapy is therefore not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of dolutegravir finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a paragraph 1 SGB V.

In the written statement, the pharmaceutical company stated that the randomised controlled ODYSSEY study (dolutegravir vs standard of care, 96 weeks) for children ≥ 4 weeks to < 6 years with HIV-1 is ongoing. The final results of the study are expected in December 2021. These final results of the ODYSSEY study are also relevant for the benefit assessment according to § 35a SGB V. In order to be able to assess these relevant data on treatment with dolutegravir on patient-relevant outcomes; it is considered sufficient to limitation of validity of this resolution until 1 April 2022.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of dolutegravir recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of

the additional benefit of dolutegravir (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). The possibility that a benefit assessment for dolutegravir can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, Nos. 2 – 6 VerfO) remains unaffected hereof. An extension of the time limit can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

2.1.5 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient dolutegravir (Tivicay®).

Dolutegravir is used in combination with other anti-retroviral medicinal products to treat human immunodeficiency virus (HIV) infections in children 4 weeks to < 6 years of age and weighing at least 3 kg.

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

a) Therapy naïve children with HIV-1 infection aged ≥ 4 weeks to < 6 years

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

For this patient group, the pharmaceutical company submits the single-arm studies IMPAACT P1093 and ODYSSEY WB-PK1/2, which justify the marketing authorisation. These studies are not relevant for the present benefit assessment, as no data are available for an assessment of dolutegravir in comparison with the appropriate comparator therapy

In the present benefit assessment procedure, no transfer of additional benefit from adults to children can be made because the conditions are not met that would justify recognition of additional benefit for children ≥ 4 weeks to < 6 years of age based on the adult results.

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 dolutegravir compared with the appropriate comparator therapy. An additional benefit is not proven.

The validity of the resolution is limited to 1 April 2022.

b) Therapy-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years

The G-BA determined an appropriate comparator therapy 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.

For this patient group, the pharmaceutical company submits the single-arm studies IMPAACT P1093 and ODYSSEY WB-PK1/2, which justify the marketing authorisation. These studies are

not relevant for the present benefit assessment, as no data are available for an assessment of dolutegravir in comparison with the appropriate comparator therapy

In the present benefit assessment procedure, no transfer of additional benefit from adults to children can be made because the conditions are not met that would justify recognition of additional benefit for children ≥ 4 weeks to < 6 years of age based on the adult results.

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 dolutegravir compared with the appropriate comparator therapy. An additional benefit is not proven.

The validity of the resolution is limited to 1 April 2022.

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

The number of patients based on a query by the pharmaceutical company of the reporting cases submitted to the Robert Koch Institute (RKI) in accordance with the Infection Protection Act from the SurvStat@RKI database[5] 2.0 is 33 children aged ≥ 0 to < 6 years who were infected with HIV in 2019. Based on data from the Federal Health Reporting, 87.8% of the population has statutory health insurance.

This results in a number of approximately 29 for the SHI target population of HIV-1 infected children aged ≥ 4 months to < 6 years.

The pharmaceutical company does not differentiate between therapy naïve and therapy-experienced children in the number of SHI patients in the target population.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Tivicay (active ingredient: dolutegravir) at the following publicly accessible link (last access: 5 March 2021):

https://www.ema.europa.eu/en/documents/product-information/tivicay-epar-product-information_de.pdf

Treatment with dolutegravir should only be initiated and monitored by doctors experienced in treating patients with HIV infection.

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 2021).

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-

[5] Robert Koch Institute. Query parameter SurvStat@RKI 2.0, query date 3.12.2020 [online]. URL: https://survstat.rki.de.

individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/subjects/year", time intervals between individual treatments and the maximum treatment duration, if specified in the product information.

Since the base therapy with which dolutegravir is to be applied does not regularly differ from the base therapy to be applied within the framework of the appropriate comparator therapy, the presentation of the treatment costs for the base therapy is omitted accordingly.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

According to the therapeutic indication, etravirine is used in combination with a boosted protease inhibitor and other anti-retroviral medicinal products. As an example, the boosted protease inhibitor lopinavir/ritonavir is used for the calculation.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 2-year-old 14.1 kg; 3-year-old 16.2 kg, 5-year-old 20.8 kg).[6] For children and infants under one year of age, the reference percentiles of the Robert Koch Institute were used. Based on the average body weights of boys and girls, the average body weight is 4.35 kg for children aged 1 month, 5.87 kg for children aged 3 months and 6.55 kg for children aged 4 months.[7]

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ subject/ year
Medicinal product to be assessed				
Dolutegravir	Once daily	365	1	365
Appropriate comparator therapy				
a) Therapy naïve children with HIV-1 infection aged ≥ 4 weeks to < 6 years				
Lopinavir/ritonavir	Twice daily	365	1	365
Raltegravir	Twice daily	365	1	365

[6]Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/
[7]Robert Koch Institute. Contributions to Federal Health Reporting Reference percentiles for anthropometric measures and blood pressure from the Study on the Health of Children and Adolescents in Germany (KiGGS) [online]. [Accessed: 9/6/2021]. URL: https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsB/KiGGS_Referenzperzentile.pdf?__blob=publicationFile.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ subject/ year
Nevirapine	Twice daily	365	1	365
b) Therapy-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years				
Lopinavir/ritonavir	Twice daily	365	1	365
Raltegravir	Twice daily	365	1	365
Nevirapine	Twice daily	365	1	365
Atazanavir + ritonavir				
Atazanavir POS + HC	Once daily	365	1	365
Ritonavir POS + FCT	Once daily	365	1	365
Darunavir + ritonavir (3 years and older)				
Darunavir OSUS + FCT	Once daily	365	1	365
Ritonavir POS + FCT	Once daily	365	1	365
Efavirenz (3 months and older)				
Efavirenz	Once daily	365	1	365
Etravirine (2 years and older)				
Etravirine	Twice daily	365	1	365
+ boosted PI Lopinavir/ritonavir	Twice daily	365	1	365
Maraviroc (2 years and older)				
Maraviroc	Twice daily	365	1	365

Consumption:

Designation of the therapy	Dosage/ Application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ Person/ year	Annual average consumption by potency
Medicinal product to be assessed					
Dolutegravir	5 mg - 30 mg	5 mg - 30 mg	1 x 5 mg - 6 x 5 mg	365	365 x 5 mg - 2,190 x 5 mg
Appropriate comparator therapy					
a) Therapy naïve children with HIV-1 infection aged ≥ 4 weeks to < 6 years					
Lopinavir/ ritonavir OS	16/4 mg/kg = 69.6/ 17.4 mg - 10/2.5 mg/kg = 208/52 mg	144/36 mg = 1.8 ml - 416/104 mg = 5.2 ml	2 x 72/18 mg = 2 x 0.9 ml - 2 x 208/52 mg = 2 x 2.6 ml	365	730 x 0.9 ml - 730 x 2.6 ml
Raltegravir Granules (only up to 20 kg BW)	30 mg - 100 mg	60 mg - 200 mg	2 x 30 mg - 2 x 100 mg	365	730 x granules sachet
Raltegravir, chewable tablets (from 11 kg BW)	75 mg 150 mg	150 mg 300 mg	6 x 25 mg - 3 x 100 mg	365	2,190 x 25 mg - 1,095 x 100 mg
Nevirapine SUS	7 mg/kg = 30.45 mg - 145.6 mg	5 ml - 30 ml	2 x 2.5 ml - 2 x 15 ml	365	730 x 2.5 ml - 730 x 15 ml
b) Therapy-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years					

Designation of the therapy	Dosage/ Application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ Person/ year	Annual average consumption by potency
Lopinavir/ ritonavir OS	16/4 mg/kg = 69.6 / 17.4 mg - 10/2.5 mg/kg = 208/52 mg	144/36 mg = 1.8 ml - 416/104 mg = 5.2 ml	2 x 72/18 mg = 2 x 0.9 ml - 2 x 208/52 mg = 2 x 2.6 ml	365	730 x 0.9 ml - 730 x 2.6 ml
Raltegravir Granules (only up to 20 kg BW)	30 mg - 100 mg	60 mg - 200 mg	2 x 30 mg - 2 x 100 mg	365	730 x granules sachet
Raltegravir, chewable tablets (from 11 kg BW)	75 mg 150 mg	150 mg 300 mg	6 x 25 mg - 3 x 100 mg	365	2,190 x 25 mg - 1,095 x 100 mg
Nevirapine SUS	7 mg/kg = 30.45 mg - 145.6 mg	5 ml - 30 ml	2 x 2.5 ml - 2 x 15 ml	365	730 x 2.5 ml - 730 x 15 ml
Atazanavir + ritonavir					
Atazanavir 90 POS	200 mg - 250 mg	200 mg - 250 mg	4 x 50 mg - 5 x 50 mg	365	1,460 x 50 mg - 1,825 x 50 mg
Ritonavir 90 POS	80 mg	80 mg	1 x 100 mg	365	365 x 100 mg
Atazanavir	200 mg	200 mg	200 mg	365	365 x 200 mg

Designation of the therapy	Dosage/ Application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ Person/ year	Annual average consumption by potency
HC (from 15 kg BW)					
Ritonavir FCT	100 mg	100 mg	100 mg	365	365 x 100 mg
Darunavir + ritonavir (3 years and older)					
Darunavir SAE	600 mg	600 mg	1 x 600 mg	365	365 x 600 mg
Ritonavir POS	100 mg	100 mg	100 mg	365	365 x 100 mg
Darunavir FCT	600 mg	600 mg	1 x 600 mg	365	365 x 600 mg
Ritonavir FCT	100 mg	100 mg	100 mg	365	365 x 100 mg
Efavirenz (3 months and older)					
Efavirenz	150 mg - 300 mg	150 mg 300 mg	1 x 100 mg + 1 x 50 mg - 3 x 100 mg	365	365 x 100 mg + 365 x 50 mg - 1,095 x 100 mg
Etravirine (2 years and older)					
Etravirine	100 mg - 125 mg	200 mg - 250 mg	2 x 100 mg - 2 x 100 mg + 2 x 25 mg	365	730 x 100 mg - 730 x 100 mg+ 730 x 25 mg
+ boosted PI: Lopinavir/ ritonavir OS	12/3 mg/kg = 169.2/ 42.3 mg -	336/84 mg=	2 x 168/42 mg =	365	730 x 2.1 ml -

Designation of the therapy	Dosage/ Application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ Person/ year	Annual average consumption by potency
	10/2.5 mg/kg = 208/252 mg	4.2 ml - 416/104 mg = 5.2 ml	2 x 2.1 ml - 2 x 208/52 mg = 2 x 2.6 ml		730 x 2.6 ml
Maraviroc (2 years and older)					
Maraviroc	50 mg - 75 mg	100 mg - 150 mg	2 x 40 mg - 2 x 80 mg	365	730 x 40 mg - 730 x 80 mg

Costs:

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

Costs of the medicinal product:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate § 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Dolutegravir	60 TSE	€ 145.13	€ 1.77	€ 0.00	€ 143.36
Appropriate comparator therapy					
Atazanavir 50 mg	30 POS	€ 158.35	€ 1.77	€ 8.16	€ 148.42
Atazanavir 200 mg	60 HC	€ 505.81	€ 1.77	€ 23.48	€ 480.56
Darunavir 100 mg/ml	200 ml SAE	€ 747.72	€ 1.77	€ 40.79	€ 705.16
Darunavir 600 mg[8]	180 FCT	€ 1,595.69	€ 1.77	€ 125.50	€ 1,468.42
Efavirenz 100 mg	30 HC	€ 82.92	€ 1.77	€ 5.62	€ 75.53

[8] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate § 130a SGB V	Costs after deduction of statutory rebates
Efavirenz 50 mg	30 HC	€ 46.99	€ 1.77	€ 1.99	€ 43.23
Etravirine 100 mg	120 TAB	€ 663.97	€ 1.77	€ 36.15	€ 626.05
Etravirine 25 mg	120 TAB	€ 205.80	€ 1.77	€ 33.97	€ 170.06
Lopinavir 80 mg/ Ritonavir 20 mg	5 x 60 ml OS	€ 792.66	€ 1.77	€ 98.91	€ 691.98
Maraviroc	230 ml OS	€ 548.48	€ 1.77	€ 29.76	€ 516.95
Nevirapine	240 ml SUS	€ 115.94	€ 1.77	€ 5.81	€ 108.36
Raltegravir 100 mg	60 GSE	€ 229.52	€ 1.77	€ 12.10	€ 215.65
Raltegravir 100mg	60 CT	€ 229.52	€ 1.77	€ 12.10	€ 215.65
Raltegravir 25 mg	60 CT	€ 65.66	€ 1.77	€ 3.02	€ 60.87
Ritonavir 100 mg	30 POS	€ 62.14	€ 1.77	€ 6.47	€ 53.90
Ritonavir 100 mg	90 FCT	€ 127.39	€ 1.77	€ 5.52	€ 120.10
Abbreviations: FCT = film-coated tablets, GOS = granules for oral suspension; HC = hard capsules; CT= chewable tablets; OS = oral solution; TOS/POS= tablet/powder for oral suspension; OSUS = oral suspension; SUS = suspension; 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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to 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 11 August 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 January 2021, the pharmaceutical company submitted a dossier for the benefit assessment of dolutegravir 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 January 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient dolutegravir.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 April 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 3 May 2021. The deadline for submitting written statements was 25 May 2021.

The oral hearing was held on 7 June 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and the 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 were discussed at the session of the subcommittee on 6 July 2021, and the proposed resolution was approved.

At its session on 15 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	11 August 2020	Determination of the appropriate comparator therapy
Working group Section 35a	2 June 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee	7 June 2021	Conduct of the oral hearing

Medicinal product		
Working group Section 35a	16 June 2021 30 June 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	6 July 2021	Concluding discussion of the draft resolution
Plenum	15 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 July 2021

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

Prof Hecken