Justification

Gemeinsamer Bundesausschuss

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

of 4 July 2019

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. Requirement 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 shall pass a resolution 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 relevant date for the first placing on the market of the active ingredient combination doravirine/lamivudine/tenofovir disoproxil in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 January 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 14 January 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 April 2019, 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, 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®) in accordance with the product information

Delstrigo® is indicated for the treatment of adults infected with the human immunodeficiency virus (HIV-1). The HI viruses must not have mutations known to be associated with resistance to the NNRTI (non-nucleosidic reverse transcriptase inhibitor) class of substances, lamivudine, or tenofovir.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Therapy-naïve adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances, lamivudine, or tenofovir

Rilpivirine in combination with tenofovir disoproxil/alafenamide plus emtricitabine or in combination with abacavir plus lamivudine

or

Dolutegravir in combination with tenofovir disoproxil/alafenamide plus emtricitabine or in combination with abacavir plus lamivudine

b) Therapy experienced adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances, lamivudine, or tenofovir

Individual anti-retroviral therapy depending on the previous therapy(ies) and taking into account the reason for the change of therapy, in particular therapy failure because of virological failure and 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 according to 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] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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 Federal Joint Committee 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 approved in principle for the treatment of adults infected with human immunodeficiency virus 1 (HIV-1):

Protease inhibitors (PI):
atazanavir, darunavir, fosamprenavir, indinavir, ritonavir, saquinavir, tipranavir, lopinavir/ritonavir

Nucleosidal and nucleotidal reverse transcriptase inhibitors (NRTI):
Abacavir, eidanosine, emtricitabine, lamivudine, stavudine, tenofovir alafenamide, tenofovir disoproxil, zidovudine

Non-nucleosidal reverse transcriptase inhibitors (NNRTI):
efavirenz, etravirine, nevirapine, rilpivirine, doravirine

Integrase inhibitors (INI):
Dolutegravir, elvitegravir, raltegravir, bictegravir

Other antiviral agents:
enfuvirtide (entry inhibitor), maraviroc (entry inhibitor)

Other therapeutic agents:
cobicistat (pharmacokinetic amplifier)

On 2. Non-medicinal treatment is not considered

On 3. Resolutions on procedures according to Section 35a SGB V:

Bictegravir/emtricitabine/tenofovir alafenamide of 20 December 2018

Dolutegravir/rilpivirine of 6 December 2018

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide of 5 July 2018

Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil of 3 May 2018

Darunavir/cobicistat/emtricitabine/tenofovir alafenamide of 16 March 2018

Dolutegravir (nAWG) of 21 September 2017

Emtricitabine/rilpivirine/tenofovir alafenamide of 5 January 2017

Emtricitabine/tenofovir alafenamide of 3 November 2016

Rilpivirine (nAWG) of 16 June 2016

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide of 16 June 2016

Dolutegravir/abacavir/lamivudine of 19 March 2015

Cobicistat of 18 September 2014

Dolutegravir of 7 August 2014

Emtricitabine/rilpivirine/tenofovir disoproxil (nAWG) of 19 June 2014

Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil of 5 December 2013

Emtricitabine/rilpivirine/tenofovir disoproxil of 5 July 2012

Rilpivirine of 5 July 2012

For the active ingredients that are part of the appropriate comparator therapy and fall within the scope of the early benefit assessment according to Section 35a SGB V, there is proof for a minor additional benefit for the treatment of HIV-infected adult patients with rilpivirine as well as for the combination emtricitabine/rilpivirine/tenofovir disoproxil (resolution of 5 July 2012). For dolutegravir, there is proof of a considerable additional benefit (resolution of 7 August 2014). For the combination dolutegravir/abacavir/lamivudine, there is an indication for a considerable additional benefit (resolution of 19 March 2015). Furthermore, for dolutegravir for therapy experienced adults for whom treatment with an integrase inhibitor is the first therapy option, there is an indication of a minor additional benefit (resolution of 7 August 2014).

On 4. The generally accepted state of medical knowledge was determined by an evidence search. For the treatment of adults infected with human immunodeficiency virus type 1 (HIV-1), the active ingredients listed under 1 are available according to the respective approved therapeutic indication. For therapy-naïve adults, the evidence search showed that the nucleosidal and nucleotidal inhibitors of the reverse transcriptase tenofovir disoproxil/tenofovir alafenamide plus emtricitabine or abacavir plus lamivudine as NRTI backbone show very good efficacy with a favourable risk profile. In addition, these are active ingredients and combinations of active ingredients for which extensive published data are available. Tenofovir disoproxil/tenofovir alafenamide plus emtricitabine and abacavir plus lamivudine are considered equally appropriate NRTI backbones for determining the appropriate comparator therapy.

The active ingredients rilpivirine and dolutegravir were determined as equally suitable combination partners for determining the appropriate comparator therapy. The background for fixing the combination partner in the appropriate comparator therapy lies in the fact that the G-BA determines a complete appropriate comparator therapy (i.e. a complete regime) based on the therapeutic indication. The choice of the two active ingredients rilpivirine or dolutegravir in combination is based on the extent, quality, and quality of the underlying body of evidence. In addition, the body of evidence of rilpivirine and dolutegravir is supported by the additional benefit in benefit assessments and resolutions of the G-BA.

When determining the appropriate comparator therapy for therapy experienced adult patients, the evidence search showed that after one or more previous therapies, depending on the active ingredient(s)/medicinal product classes used and the reason for the change in 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.

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 doravirine/lamivudine/tenofovir disoproxil (DOR/3TC/TDF) is assessed as follows:

a) Therapy-naïve adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances, lamivudine, or tenofovir

An additional benefit is not proven.

Justification:

In the double-blind, randomised parallel group study on HIV-1-infected adults (021), which justified the approval, there was no implementation of the appropriate comparator therapy. For the assessment of the additional benefit of DOR/3TC/TDF, three RCTs were submitted for one adjusted indirect comparison of DOR/3TC/TDF (study 021) with dolutegravir (DTG) in combination with 2 NRTI (SINGLE and SPRING-1 studies) via the bridge comparator efavirenz (EFV).

In Study 021 DOR/3TC/TDF was compared with EFV/emtricitabine (FTC)/TDF. In Study 021, a total of 734 patients were assigned to treatment with DOR/3TC/TDF (N = 368) or EFV/FTC/TDF (N = 366) at a ratio of 1:1.

The SINGLE and SPRING-1 studies are randomised parallel group studies. The SINGLE study was double-blind, and the SPRING-1 study partially blinded.

In the SINGLE study, DTG + ABC/3TC was compared with EFV/FTC/TDF. In the SINGLE study, a total of 844 patients were randomised at a ratio of 1:1 for treatment with DTG + ABC/3TC (N = 422) or EFV/FTC/TDF (N = 422).

The SPRING-1 study is a dose-finding study on DTG. Only patients from the study arm in which the daily dose of 50 mg DTG (N = 51) for adults was administered according to the product information are included in the present benefit assessment. The patients in the comparator arm (N = 52) received EFV. The study was open with respect to the patient allocation to DTG or EFV; only the daily dose of DTG was blinded. In addition to the study medication, the patients received a base therapy of either TDF/FTC or ABC/3TC.

In RCTs 021, SINGLE, and SPRING-1, the HIV-1 ribonucleic acid (RNA) virus load of the patients had to be ≥ 1000 copies/ml for screening. In all studies, the randomised treatment duration was 96 weeks.

Virological response (HIV-1 RNA < 50 copies/ml) was the primary endpoint in all three studies. Other patient-relevant endpoints were mortality, morbidity, and adverse events (AE). Data on health-related quality of life was not collected in any of the studies.

The data available for the study and intervention characteristics of the three studies show that the studies are sufficiently similar with regard to the design and the bridge comparator used. The influence of the partially different base therapies of 2 NRTI on the results of the indirect comparison is considered negligible.

For the present benefit assessment, the results at the time of evaluation of 96 weeks are used.

Extent and probability of the additional benefit

Mortality

For the endpoint overall survival, the adjusted indirect comparison showed no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI. Thus, an additional benefit of DOR/3TC/TDF compared with DTG + 2 NRTI is not proven for the endpoint mortality.

Morbidity

AIDS-defining events (CDC class C)

The endpoint AIDS-defining events (CDC class C) is mainly composed of opportunistic infections (e.g. pneumonia) and typical tumours (e.g. Kaposi's sarcoma, lymphoma) that manifest the occurrence of AIDS. The aim of any anti-retroviral therapy is to prevent the occurrence of the events summarised in the endpoint AIDS-defining events and thus the outbreak of AIDS. The endpoint therefore enables the evaluation of the therapeutic success with regard to the prevention of AIDS-defining diseases and is thus directly relevant to the patient.

In accordance with the CDC definition[2] of the endpoint AIDS-defining events, a low CD4 cell count (< 200 cells/µl) also counts as a predefined endpoint event.

In addition to the valid surrogate parameters viral load and CD4 cell count, the AIDS-defining events also represent a relevant efficacy endpoint for EMA in the present indication. The use of the CDC classification is considered appropriate; however, the CD4 cell count is excluded as an AIDS-defining event.[3]

The occurrence of AIDS-defining events within the first months after the initiation of therapy may not be considered to be the result of insufficient efficacy of the therapy but can also be based on the immunodeficiency at the time of initiation of therapy, which is highly advanced in individual patients. These AIDS-defining events therefore only become apparent in connection with a therapy-related recovery of the immune system (immune reconstitution syndrome or IRIS) and can thus also be an expression of the therapeutic success.

For the endpoint AIDS-defining events (CDC class C), the adjusted indirect comparison showed no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI.

Virological response

The validated surrogate parameter "Virological response (viral load)" is patient-relevant.

For the effects on the endpoint virological response, the pharmaceutical company presented the evaluation according to the Snapshot algorithm (except for the SPRING-1 study) in the dossier. Evaluation using the Snapshot algorithm is a possible option for assessing whether the HIV RNA viral load was below the detection limit of < 50 copies/ml in a predefined evaluation window. The SPRING-1 study was also evaluated using the Time to Loss of Virologic Response (TLOVR) algorithm with the separation value of 50 HIV-1 RNA copies/ml. The analysis types Snapshot and TLOVR differ in particular with regard to the handling of missing values and the definition of virological response/failure. Because these different types of evaluation in the benefit assessment for dolutegravir did not lead to relevant deviations in the results of the meta-analysis for this endpoint, the results for this endpoint are also included in the adjusted indirect comparison in the present benefit assessment.

For the endpoint virological response, the adjusted indirect comparison showed no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI.

CD4 cell counts

The endpoint CD4 cell count is highly important for the diagnosis and therapy planning of HIV infection as well as for the planning and evaluation of studies in the indication HIV infection.

[2] CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992; 41 (no. RR-17).
[3] Guideline on the clinical development of medicinal products for the treatment of HIV-Infection EMA 2008.

The reduction of CD4 cell counts below normal physiological levels is an indicator of immunodeficiency and a consequence of the harmful effect of the HI virus by binding to the CD4 receptors of the CD4 cell.

In Study 021 and the SPRING-1 study, the endpoint CD4 cell count has a high risk of bias (violation of the ITT principle). Therefore, neither an advantage nor a disadvantage of DOR/3TC/TDF compared with DTG + 2 NRTI can be derived for this endpoint.

In the summary of the results on AIDS-defining diseases, virological response, and CD4 cell count, an additional benefit of DOR/3TC/TDF compared with DTG + 2 NRTI is not proven for the endpoint morbidity.

Quality of life

In study 021 as well as the SINGLE and SPRING-1 studies, endpoints of the endpoint category health-related quality of life were not investigated. Thus, an additional benefit of DOR/3TC/TDF compared with DTG + 2 NRTI is not proven for the endpoint quality of life.

Side effects

For the endpoints serious adverse events (SAE) and severe adverse events (AE; Division of AIDS (DAIDS) grade 3–4), no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI was found in the adjusted indirect comparison.

For the endpoint withdrawal because of AEs, the adjusted indirect comparison showed no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI.

For the endpoint specific AEs, the pharmaceutical company submitted incomplete evaluations both in the dossier and in the written statement procedure. These were not taken into account for the benefit assessment. Thus, neither statistically significant advantages nor disadvantages of DOR/3TC/TDF compared with DTG + 2 NRTI can be derived for this endpoint.

In the category side effects, there were no statistically significant differences between DOR/3TC/TDF and DTG + 2 NRTI in the overall view.

Overall assessment/conclusion

For the benefit assessment of doravirine/lamivudine/tenofovir disoproxil for the treatment of therapy-naïve adult patients infected with HIV-1, an adjusted indirect comparison of DOR/3TC/TDF (study 021) with dolutegravir (DTG) in combination with 2 NRTI (SINGLE and SPRING-1 studies) via the bridge comparator efavirenz (EFV) was presented. The adjusted indirect comparison yields results on mortality, morbidity, and side effects. No health-related quality of life survey was carried out in the studies.

For the endpoint overall survival, the adjusted indirect comparison showed no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI.

In the overall view of the results in the morbidity category on AIDS-defining diseases, virological response, and CD4 cell count, an additional benefit of DOR/3TC/TDF compared with DTG + 2 NRTI is not proven.

In the category side effects, there were no statistically significant differences between the treatment arms in the adjusted indirect comparison.

In summary, the overall results for mortality, morbidity, and adverse events in therapy-naïve adult patients infected with HIV-1 show no additional benefit for DOR/3TC/TDF compared with DTG + 2 NRTI.

b) Therapy experienced adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances, lamivudine, or tenofovir

An additional benefit is not proven.

Justification:

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 DOR/3TC/TDFcompared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Delstrigo® with the active ingredient combination doravirine/lamivudine/tenofovir disoproxil (DOR/3TC/TDF). DOR/3TC/TDF is indicated for the treatment of adults infected with the human immunodeficiency virus (HIV-1). The HI viruses must not have mutations known to be associated with resistance to the NNRTI (non-nucleosidic reverse transcriptase inhibitor) class of substances, lamivudine, or tenofovir.

In the therapeutic indication to be considered, two patient groups were distinguished: a) Therapy-naïve adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances, lamivudine, or tenofovir and b) Therapy experienced adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances, lamivudine, or tenofovir.

a) Therapy-naïve adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances, lamivudine, or tenofovir

In the double-blind, randomised parallel group study on HIV-1-infected adults (021), which justified the approval, there was no implementation of the appropriate comparator therapy. For the assessment of the additional benefit of DOR/3TC/TDF, three RCTs were submitted for one adjusted indirect comparison of DOR/3TC/TDF (study 021) with dolutegravir (DTG) in combination with 2 NRTI (SINGLE and SPRING-1 studies) via the bridge comparator efavirenz (EFV).

The data available for the study and intervention characteristics of the three studies show that the studies are sufficiently similar with regard to the design and the bridge comparator used. The influence of the partially different base therapies of 2 NRTI on the results of the indirect comparison is considered negligible.

The adjusted indirect comparison yields results on mortality, morbidity, and side effects. No health-related quality of life survey was carried out in the studies.

For the endpoint overall survival, the adjusted indirect comparison showed no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI.

In the overall view of the results in the morbidity category on AIDS-defining diseases, virological response, and CD4 cell count, an additional benefit of DOR/3TC/TDF compared with DTG + 2 NRTI is not proven.

In the category side effects, there were no statistically significant differences between the treatment arms in the adjusted indirect comparison.

In summary, the overall results for mortality, morbidity, and adverse events in therapy-naïve adult patients infected with HIV-1 show no additional benefit for DOR/3TC/TDF compared with DTG + 2 NRTI.

b) Therapy experienced adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances, lamivudine, or tenofovir

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 DOR/3TC/TDF compared with the appropriate comparator therapy.

In the overall view, an additional benefit for DOR/3TC/TDF for therapy-experience adult patients infected with HIV-1 is not proven.

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

a) Therapy-naïve adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances, lamivudine, or tenofovir

Based on the data from the Robert Koch Institute (RKI)[4], the pharmaceutical company assumes that 3200–3500 newly infected patients (estimated incidence in 2017) as well as an estimated 3000–9300 diagnosed patients not yet treated with anti-retroviral therapy (ART) at the end of 2017 will be treated. The 3,000–9,300 patients result from 69,000–80,900 patients with a HIV diagnosis and 66,000–71,600 patients with ART. Patients not yet diagnosed (11,400) are not included in the calculation of the pharmaceutical company.

Based on three German cohort studies and according to the pharmaceutical company, 2.6% of patients show primary resistance to non-nucleosidic reverse transcriptase inhibitors (NNRTI) and 5.9% primary resistance to NRTI and are therefore not eligible for the administration of doravirine/lamivudine/tenofovir disoproxil.

Furthermore, the therapy should not be initiated in patients with a creatinine clearance of < 50 ml/min. The pharmaceutical company therefore refers to a share value of 1.6% of the patients who should also not be considered for the administration of doravirine/lamivudine/tenofovir disoproxil.

Assuming that 87.1% of the German population is covered by statutory health insurance, approx. 4,855–10,023 therapy-naïve adult SHI patients are eligible for the administration of doravirine/lamivudine/tenofovir disoproxil.

b) Therapy experienced adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances, lamivudine, or tenofovir

Based on the data on patient numbers from the Robert Koch Institute (RKI)[4], the pharmaceutical company assumes that 66,000–71,600 patients will be treated with anti-retroviral therapy (ART).

[4] Robert Koch Institute. Epidemiological Bulletin 47/2018.

Based on three German cohort studies and according to the pharmaceutical company, 2.6–11.4% of patients show resistance mutations to non-nucleosidic reverse transcriptase inhibitors (NNRTI) and 5.9–12.9% resistance mutations to NRTI and are therefore not eligible for the administration of doravirine/lamivudine/tenofovir disoproxil.

Furthermore, the therapy should not be initiated in patients with a creatinine clearance of < 50 ml/min. The pharmaceutical company therefore refers to a share value of 1.6% of the patients who should also not be considered for the administration of doravirine/lamivudine/tenofovir disoproxil.

Assuming that 87.1% of the German population is covered by statutory health insurance, according to the pharmaceutical company approx. 43,940–57,968 patients are eligible for the administration of doravirine/lamivudine/tenofovir disoproxil.

There are uncertainties in the assumptions made by the pharmaceutical company regarding resistance frequencies. Furthermore, it is not clear to what extent the underlying populations for resistance assessment are representative of the SHI target population. As a result, the number of patients indicated is overestimated.

2.3 Requirements for a quality-assured application

The requirements of 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 combination: doravirine/lamivudine/tenofovir disoproxil) at the following publicly accessible link (last access: 27 May 2019):

https://www.ema.europa.eu/documents/product-information/delstrigo-epar-product-information_de.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

For the calculation of medicinal product costs, the number of packages required based on potency was initially used. Based on the determined number of packages required, the medicinal product costs were then calculated based on the costs per package after deducting the statutory rebates. In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Section 130a SGB V (paragraph 1, 1a, 3a) and Section 130, paragraph 1 SGB V.

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.

For the appropriate comparator therapy of adults with previous anti-retroviral 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 (maraviroc + abacavir + emtricitabine) as an example.

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

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 June 2019).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/ year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Doravirine/lamivudine/ tenofovir disoproxil	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
Rilpivirine + emtricitabine/tenofovir disoproxil				
Rilpivirine	continuously, 1 × daily	365	1	365
Emtricitabine/tenofovir disoproxil	continuously, 1 × daily	365	1	365

[5] German-Austrian guidelines for anti-retroviral therapy of HIV infection (consented Version 2017)

Designation of the therapy	Treatment mode	Number of treatments/patient/ year	Treatment duration/treatment (days)	Treatment days/patient/ year
Rilpivirine + emtricitabine/tenofovir alafenamide				
Rilpivirine	continuously, 1 × daily	365	1	365
Emtricitabine/tenofovir alafenamide	continuously, 1 × daily	365	1	365
Rilpivirine + abacavir/lamivudine				
Rilpivirine	continuously, 1 × daily	365	1	365
Abacavir/lamivudine	continuously, 1 × daily	365	1	365
Dolutegravir + emtricitabine/tenofovir disoproxil				
Dolutegravir	continuously, 1 × daily	365	1	365
Emtricitabine/tenofovir disoproxil	continuously, 1 × daily	365	1	365
Dolutegravir + emtricitabine/tenofovir alafenamide				
Dolutegravir	continuously, 1 × daily	365	1	365
Emtricitabine/tenofovir alafenamide	continuously, 1 × daily	365	1	365
Dolutegravir/abacavir/lamivudine				
Dolutegravir/abacavir/lamivudine	continuously, 1 × daily	365	1	365
Patient population b)				
Nevirapine + emtricitabine/tenofovir disoproxil				

Designation of the therapy	Treatment mode	Number of treatments/patient/ year	Treatment duration/treatment (days)	Treatment days/patient/ year
Nevirapine	continuously, 2 × daily	365	1	365
Emtricitabine/tenofovir disoproxil	continuously, 1 × daily	365	1	365
Maraviroc + abacavir + emtricitabine				
Maraviroc	continuously, 2 × daily	365	1	365
Abacavir	continuously, 2 × daily	365	1	365
Emtricitabine	continuously, 1 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/application	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/patient year	annual average 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 × 100 mg/300 mg/245 mg	365	365 × 100 mg/300 mg/245 mg
Appropriate comparator therapy					
Patient population a)					
Rilpivirine + emtricitabine/tenofovir disoproxil					
Rilpivirine	25 mg	25 mg	1 × 25 mg	365	365 × 25 mg

Designation of the therapy	Dosage/application	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/patient year	annual average consumption by potency
Emtricitabine/tenofovir disoproxil	200 mg/245 mg	200 mg/245 mg	1 × 200 mg/245 mg	365	365 × 200 mg/245 mg
Rilpivirine + emtricitabine/tenofovir alafenamide					
Rilpivirine Emtricitabine/tenofovir alafenamide	25 mg 200 mg/25 mg	25 mg 200 mg/25 mg	1 × 25 mg 1 × 200 mg/25 mg	365 365	365 × 25 mg 365 × 200 mg/25 mg
Rilpivirine + abacavir/lamivudine					
Rilpivirine Abacavir/lamivudine	25 mg 600mg/300 mg	25 mg 600 mg/300 mg	1 × 25 mg 1 × 600 mg/1 × 300 mg	365 365	365 × 25 mg 365 × 600 mg/300 mg
Dolutegravir + emtricitabine/tenofovir disoproxil					
Dolutegravir Emtricitabine/ tenofovir disoproxil	50 mg 200 mg/245 mg	50 mg 200 mg/245 mg	1 × 50 mg 1 × 200 mg/245 mg	365 365	365 × 50 mg 365 × 200 mg/245 mg
Dolutegravir + emtricitabine/tenofovir alafenamide					
Dolutegravir Emtricitabine/tenofovir alafenamide	50 mg 200 mg/25 mg	50 mg 200 mg/25 mg	1 × 50 mg 1 × 200 mg/25 mg	365 365	365 × 50 mg 365 × 200 mg/25 mg
Dolutegravir/abacavir/lamivudine					
Dolutegravir/ Abacavir/lamivudine	50 mg/600 mg/300 mg	50 mg/600 mg/300 mg	1 × 50 mg/600 mg/300 mg	365	365 × 50 mg/600 mg/300 mg
Patient population b)					
Nevirapine + emtricitabine/tenofovir disoproxil					
Nevirapine	200 mg	400 mg	2 × 200 mg	365	730 × 200 mg

Designation of the therapy	Dosage/application	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/patient year	annual average consumption by potency
Emtricitabine/tenofovir disoproxil	200 mg/245 mg	200 mg/245 mg	1 × 200 mg/245 mg	365	365 × 200 mg/245 mg
Maraviroc + abacavir + emtricitabine					
Maraviroc	300 mg	600 mg	2 × 300 mg	365	730 × 300 mg
Abacavir	300 mg	600 mg	2 × 300 mg	365	730 × 300 mg
Emtricitabine	200 mg	200 mg	1 × 200 mg	365	365 × 200 mg

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Doravirine/lamivudine/ tenofovir disoproxil	90 PFS	€2,484.21	€1.77	€138.60	€2,343.84
Appropriate comparator therapy					
Patient population a)					
Dolutegravir	90 PFS	€2,134.88	€1.77	€0.00	€2,133.11
Dolutegravir/ Abacavir/lamivudine	90 PFS	€2,925.46	€1.77	€0.00	€2,923.69
Emtricitabine/tenofovir disoproxil	35 PFS	€56.00	€1.77	€2.14	€52.09
Emtricitabine/tenofovir alafenamide	90 PFS	€1,561.47	€1.77	€85.90	€1,473.80
Abacavir/lamivudine	30 PFS	€478.20	€1.77	€22.17	€454.36
Rilpivirine	30 PFS	€374.22	€1.77	€0.00	€372.45
Patient population b)					
Abacavir 300 mg	60 PFS	€348.55	€1.77	€16.02	€330.76
Emtricitabine	30 HC	€302.41	€1.77	€18.63	€282.01

Designation of the therapy	Package size	Costs (pharmacy wholesale price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Emtricitabine/tenofovir disoproxil	35 PFS	€56.00	€1.77	€2.14	€52.09
Maraviroc	60 PFS	€1,073.00	€1.77	€58.80	€1,012.43
Nevirapine	120 TAB	€267.63	€1.77	€13.34	€252.52
Abbreviations: FCT = film-coated tablets, HC = hard capsules, TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 June 2019

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

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 December 2017.

On 14 January 2019, 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 14 January 2019 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 combination doravirine/lamivudine/tenofovir disoproxil.

The dossier assessment by the IQWiG was submitted to the G-BA on 14 January 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 April 2019. The deadline for submitting written statements was 6 May 2019.

The oral hearing was held on 27 May 2019.

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 statements received and the oral hearing were discussed at the session of the subcommittee on 24 June 2019, and the proposed resolution was approved.

At its session on 4 July 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 December 2017	Determination of the appropriate comparator therapy
Working group Section 35a	22 May 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 May 2019	Conduct of the oral hearing
Working group Section 35a	5 June 2019 19 June 2019	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	25 June 2019	Concluding discussion of the proposed resolution
Plenum	4 July 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 July 2019

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

Prof Hecken