Justification

Gemeinsamer Bundesausschuss

to 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/Lamivudine

of 6 February 2020

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 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 dolutegravir/lamivudine in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 August 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 3 July 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 2019 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 dolutegravir/lamivudine compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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/lamivudine.

[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.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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/lamivudine (Dovato®) in accordance with the product information

Dovato is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Therapy naïve adult HIV-1 patients who have no known or suspected resistance to the integrase inhibitor class or lamivudine.

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 who have no known or suspected resistance to the integrase inhibitor class or lamivudine

A patient-individual antiretroviral 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 possible associated development of resistance or because of side effects.

c) Therapy naïve adolescent HIV-1 patients above 12 years who have no known or suspected resistance to the integrase inhibitor class or lamivudine

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

or

Dolutegravir in combination with tenofovir alafenamide plus emtricitabine or in combination with abacavir plus lamivudine.

d) Therapy experienced adolescent HIV-1 patients above 12 years who have no known or suspected resistance to the integrase inhibitor class or lamivudine

A patient-individual antiretroviral 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 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. 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[2] 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:

[2] For adolescents from the age of 12 years, the active ingredients listed for adults are also approved with the exception of the following active ingredients: saquinavir, doravirine, bictegravir

Doravirine/lamivudine/tenofovir disoproxil of 4 July 2019
Doravirine of 4 July 2019
Bictegravir/emtricitabine/tenofovir alafenamide of 20 December 2018
Dolutegravir/rilpivirine of 6 December 2018
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (new therapeutic indication) of 5 July 2018
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil (new therapeutic indication) of 3 May 2018
Darunavir/cobicistat/emtricitabine/tenofovir alafenamide of 16 March 2018
Dolutegravir (new therapeutic indication) of 21 September 2017
Emtricitabine/rilpivirine/tenofovir alafenamide of 5 January 2017
Emtricitabine/tenofovir alafenamide of 3 November 2016
Rilpivirine (new therapeutic indication) 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 (new therapeutic indication) 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 and adolescents above 12 years of age[2] 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 adolescents from the age of 12 years as well as 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 following restriction applies to the treatment of adolescents: Tenofovir disoproxil should be used in non-pretreated adolescents from the age of 12 years only if the use of first-line medicinal products is excluded because of resistance to NRTI or intolerance. Tenofovir disoproxil is therefore out of the question when determining the appropriate comparator therapy for therapy naïve adolescents aged 12 years and older.

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 adolescents from the age of 12 years and 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 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.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

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

a) Therapy naïve adult HIV-1 patients who have no known or suspected resistance to the integrase inhibitor class or lamivudine

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit for the patient group of non-antiretrovirally pre-treated (therapy naïve) adults (≥ 18 years), the results of the meta-analysis of the two double-blind, parallel, randomised controlled studies, GEMINI-1 and GEMINI-2, are generally used.

Upon submission of the dossier, data for week 48 were available for both studies; in the course of the written statement procedure, the pharmaceutical company submitted a further data cut-off at week 96 for both studies. For the benefit assessment, the evaluation in the addendum of the IQWiG to the data cut-off of week 96 is decisive.

In both studies presented, dolutegravir/lamivudine (DTG/3TC) was compared with the specific appropriate comparator therapy DTG in combination with tenofovir disoproxil/emtricitabine (TDF/FTC).

Patients were randomised to the intervention arm or the comparator arm at a ratio of 1:1. A total of 719 patients were included in the GEMINI-1 study; 359 patients received DTG/3TC, and 360 patients received DTG in combination with TDF/FTC. In the GEMINI-2 study, out of 722 patients, 360 patients were assigned to treatment with DTG/3TC and 362 patients to therapy with DTG in combination with TDF/FTC.

In both studies, patients were stratified according to HIV-1 RNA viral load and CD4 cell count.

According to the pharmaceutical company, the screening for resistance to HIV is based on the recommendations of the International Antiviral Society USA panel. Accordingly, patients who showed signs of the listed resistances at the time of screening or before were excluded from participating in the study.

Virological response (HIV-1 RNA < 50 copies/ml) at week 48 was the primary endpoint in both 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.

Extent and probability of the additional benefit

Mortality

In the GEMINI-1 and GEMINI-2 studies, there was no statistically significant difference between the treatment groups for the overall survival endpoint. Thus, an additional benefit of DTG/3TC compared with DTG + TDF/FTC is not proven for the mortality endpoint.

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 antiretroviral 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[3] 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.[4]

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 AIDS-defining events endpoint of Class CDC, the meta-analysis showed no statistically significant difference between the treatment groups.

Virological response/virological failure

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

For the presentation of the effects on the endpoint virological response or virological failure, the pharmaceutical company chose to use the snapshot algorithm 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.

For the endpoints virological response and virological failure, there is no statistically significant difference between treatment groups for the total population in the meta-analysis.

For the endpoint virological response, there is proof of effect modification by the characteristic CD4 cell count at the start of study. For patients with a CD4 cell count ≤ 200 cells/mm³ at the

[3] 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).
[4] Guideline on the clinical development of medicinal products for the treatment of HIV-Infection EMA 2008.

start of study, there is a statistically significant disadvantage of DTG/3TC compared with DTG + TDF/FTC. For patients with a CD4 cell count > 200 cells/mm³ at the start of study, there is no statistically significant difference between the treatment groups.

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. 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.

For the CD4 cell count, the meta-analysis of the GEMINI-1 and GEMINI-2 studies showed no statistically significant difference between the treatment arms.

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

Health status measured with the EQ-5D VAS

For the health status endpoint surveyed with the EQ-5D VAS, no meta-analysis is between the GEMINI-1 and GEMINI-2 studies is presented because of heterogeneity without unidirectional effects. The GEMINI-1 study shows a statistically significant difference in favour of DTG/3TC, while the GEMINI-2 study shows no statistically significant difference between the treatment groups. An additional benefit is thus not proven for this endpoint.

Quality of life

In the GEMINI-1 and GEMINI-2 studies, endpoints of the endpoint category health-related quality of life were not investigated. Thus, an additional benefit of DTG/3TC compared with DTG + TDF/FTC is not proven for the quality of life endpoint.

Side effects

For the endpoints serious adverse events (SAE), severe adverse events (AE; Division of AIDS (DAIDS) grades 3–4) and discontinuation because of AEs, the meta-analysis showed no statistically significant difference between DTG/3TC and DTG + TDF/FTC.

In the specific AEs, the endpoints nasopharyngitis (PT), arthralgia (PT), and nausea (PT) each showed a statistically significant advantage of DTG/3TC compared with DTG + TDF/FTC. Overall, the events were not serious/not severe. For the other specific AEs, the meta-analysis showed no statistically significant difference between the treatment groups. Taking into account the clinical symptomatology and severity of the disease as well as the type and frequency of occurrence of the AEs, the advantages for the specific AEs are estimated to be the non-relevant reduction of side effects.

In the side effects category, there are no clinically relevant differences between DTG/3TC compared with DTG + TDF/FTC.

Overall assessment/conclusion

The two double-blind, parallel, randomised controlled trials GEMINI-1 and GEMINI-2 were presented to assess the extent of the additional benefit of DTG/3TC. Results on mortality, morbidity, and side effects are available. No health-related quality of life survey was carried out in the studies.

For the overall survival endpoint, there was no statistically significant difference between DTG/3TC and DTG + TDF/FTC.

In the overall review of the results of the morbidity category on AIDS-defining diseases, virological response, virological failure, CD4 cell count, and health status, an additional benefit of DTG/3TC compared with DTG + TDF/FTC is not proven.

In the side effects category, the meta-analysis showed no statistically significant difference between the treatment groups for the endpoints SAE, severe AEs and discontinuation because of AEs.

At the level of individual specific AEs (nasopharyngitis, arthralgia, nausea), a statistically significant difference in favour of DTG/3TC can be determined in each case. Overall, the events were not serious/not severe. Taking into account the clinical symptomatology and the severity of the disease as well as the type and frequency of occurrence of the AEs, this advantage is not considered to be a relevant reduction of side effects and therefore does not lead to the derivation of an additional benefit.

In the side effects category, there are therefore no differences between DTG/3TC and DTG + TDF/FTC relevant for the benefit assessment.

In summary, in the overall assessment of the results on mortality, morbidity, and side effects, there is no additional benefit of dolutegravir/lamivudine compared with dolutegravir and tenofovir disoproxil/emtricitabine for therapy naïve adult HIV-1 patients.

b) Therapy experienced adult HIV-1 patients who have no known or suspected resistance to the integrase inhibitor class or lamivudine.

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit for the patient group of antiretrovirally pretreated (therapy experienced) adults, the pharmaceutical company will present the two open, parallel, randomised controlled ASPIRE studies as well as the TANGO study in the dossier.

The results of the TANGO study were not submitted by the pharmaceutical company until after the written statement procedure. A meta-analytical summary of the ASPIRE and TANGO studies was not submitted, although this would have been possible in principle. In the following, the results of the two studies are considered separately.

In the studies, treatment with dolutegravir/lamivudine was compared with a continuation of the previous antiretroviral therapy (ART).

At least 48 weeks before the start of study, the HIV-1 ribonucleic acid (RNA) viral load of the patients had to be < 50 copies/ml in both studies and additionally < 20 copies/ml at the time of enrolment in the ASPIRE study.

The studies included pretreated HIV-1-infected adults who had been treated continuously for at least 48 weeks with an antiretroviral therapy regimen of three active ingredients. Only TAF-based therapies were included in the TANGO study.

In the ASPIRE study, no resistance to the group of integrase inhibitors and no mutations in the protease or reverse transcriptase gene should have been present in patients at the start of study. In the TANGO study, patients who showed signs of resistance before or at the time of

screening in accordance with the recommendation of the International Antiviral Society US Panel were excluded.

Patients were randomised to the intervention arm or the comparator arm at a ratio of 1:1. In the ASPIRE study, out of a total of 90 patients, 45 patients were assigned to treatment with dolutegravir/lamivudine, and 45 patients were assigned to continuation of the previous therapy. In the TANGO study, out of a total of 743 patients, 371 patients were assigned to treatment with dolutegravir/lamivudine, and 372 patients were assigned to continuation of the previous TAF-based therapy and stratified according to the third component of ART.

Virological failure (HIV-1 RNA ≥ 50 copies/ml) was the primary endpoint in the ASPIRE study at week 24 as well as in the TANGO study at week 48. Other patient-relevant endpoints were mortality, morbidity, and adverse events (AE). Data on health-related quality of life were not collected in the study. The assessment of both studies is based on the data cut-offs at week 48.

It is assumed that the studies predominantly included patients for whom there was no medically necessary changeover indication of the existing previous therapy. Thus, for these patients, the continuation of the previous therapy in the control arm of both studies corresponds to the appropriate comparator therapy. The results of the study can be used to assess the additional benefit in pretreated adults without changeover indication.

In contrast, no data are available for pretreated adult patients with a changeover indication. It is therefore not possible to assess the additional benefit for these patients.

Extent and probability of the additional benefit

Mortality

In the ASPIRE and TANGO studies, there was no statistically significant difference between the treatment groups for the overall survival endpoint. Thus, an additional benefit of DTG/3TC compared with continuation of the existing ART is not proven for the mortality endpoint.

Morbidity

AIDS-defining events (CDC class C) and health status (EQ-5D VAS)

For the endpoints AIDS-defining events and health status, the TANGO study showed no statistically significant difference between the treatment arms. Data for these endpoints are not available in the ASPIRE study.

Virological response, virological failure, and CD4 cell count

For the endpoints virological response and CD4 cell count, there was no statistically significant difference between the treatment arms in either study. No results for virological failure were available from the ASPIRE study. In the TANGO study, there was no statistically significant difference between the treatment arms.

In the summary of the results on AIDS-defining diseases, virological response, virological failure, CD4 cell count, and health status, an additional benefit of DTG/3TC compared with the continuation of existing ART is not proven for the morbidity endpoint.

Quality of life

In the ASPIRE and TANGO studies, endpoints of the endpoint category health-related quality of life were not investigated. Thus, an additional benefit of DTG/3TC compared with continuation of the existing ART is not proven for the quality of life endpoint.

Side effects

In the ASPIRE study, there were no statistically significant difference between the treatment groups for the endpoints serious adverse events (SAE) and discontinuation because of AEs. For the endpoint severe adverse events (AE; Division of AIDS (DAIDS) Grades 3–4) no usable data are available because of possible multiple entries. No results are available for the specific Aes endpoint.

In the TANGO study, there was no statistically significant difference between the treatment groups for the endpoints SAEs and severe AEs (DAIDS grade 3–4). For the endpoints discontinuation because of AEs, fatigue (PT), and seasonal allergy (PT), there was a statistically significant difference to the detriment of DTG/3TC. Most of the events that occurred were not classified as serious.

Overall assessment/conclusion

Overall, no data are available for patients with changeover indications.

For patients without a changeover indication, the ASPIRE and TANGO studies provide results on mortality, morbidity, and side effects. No health-related quality of life survey was carried out in the studies.

The ASPIRE study shows no significant differences. From the TANGO study, statistically significant differences to the detriment of dolutegravir/lamivudine were found for patients without changeover indication in the endpoints discontinuation because of AEs as well as fatigue (PT) and seasonal allergy (PT).

Overall, it is questionable whether in clinical practice there will be a changeover from the previous therapy for patients for whom there are no medical reasons for a change of therapy. A clear demarcation between patients with and without changeover indication is not directly transferable to the everyday health care situation. In addition, the transferability of the results of the patient group without changeover indication to the overall population of therapy experienced adults is unclear.

The additional benefit is therefore assessed for the total population of therapy experienced adults.

Because the results thus only apply to a subgroup of this patient group, whose relevance for everyday care is questionable, no additional benefit or lower benefit of dolutegravir/lamivudine compared with the appropriate comparator therapy can be derived for the overall population from the data on side effects.

In summary, in the overall assessment of the results on mortality, morbidity, and side effects, there is no additional benefit of dolutegravir/lamivudine compared with the appropriate comparator therapy for pretreated HIV-1-infected adult patients.

c) Therapy naïve adolescent HIV-1 patients above 12 years who have no known or suspected resistance to the integrase inhibitor class or lamivudine

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 dolutegravir/lamivudine compared with the appropriate comparator therapy.

d) Therapy experienced adolescent HIV-1 patients above 12 years who have no known or suspected resistance to the integrase inhibitor class or lamivudine

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 dolutegravir/lamivudine compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment concerts the benefit assessment of the new medicinal product Dovato® with the active ingredient combination dolutegravir/lamivudine (DTG/3TC). DTG/3TC indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.

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

a) Therapy naïve adult HIV-1 patients who have no known or suspected resistance to the integrase inhibitor class or lamivudine;
b) Therapy experienced adult HIV-1 patients who have no known or suspected resistance to the integrase inhibitor class or lamivudine;
c) Therapy naïve adolescent HIV-1 patients above 12 years who have no known or suspected resistance to the integrase inhibitor class or lamivudine;
d) Therapy experienced adolescent HIV-1 patients above 12 years who have no known or suspected resistance to the integrase inhibitor class or lamivudine.

a) Therapy naïve adult HIV-1 patients who have no known or suspected resistance to the integrase inhibitor class or lamivudine

Rilpivirine or dolutegravir (DTG), each in combination with tenofovir disoproxil/alafenamide (TDF/TAF) plus emtricitabine (FTC) or in combination with abacavir plus lamivudine, were determined to be appropriate comparator therapies by the G-BA. By directly comparing DTG/3TC with DTG + TDF/FTC, this appropriate comparator therapy was implemented in the two pivotal double-blind, randomised parallel group studies GEMINI-1 and GEMINI-2 in HIV-1-infected adults.

In the mortality and morbidity categories, the meta-analysis shows no statistically significant difference between the treatment groups. There was no survey of health-related quality of life.

In the side effects category, there are no statistically significant differences in serious AEs, severe AEs (DAIDS grade 3–4), and discontinuation because of AEs. At the level of individual specific AEs (nasopharyngitis, arthralgia, nausea), a statistically significant difference in favour of DTG/3TC can be determined. Taking into account the clinical symptomatology and the severity of the disease, this advantage is not considered to be a relevant reduction of side effects and therefore does not lead to the derivation of an additional benefit.

In summary, in the overall assessment of the results, for therapy naïve adult patients infected with HIV-1, there is no additional benefit for DTG/3TC compared with DTG + TDF/FTC.

b) Therapy experienced adult HIV-1 patients who have no known or suspected resistance to the integrase inhibitor class or lamivudine

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(ies) and 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. By comparing DTG/3TC with the continuation of the previous therapy, this appropriate comparator therapy will be implemented in the two open, randomised parallel group studies ASPIRE and TANGO on adult HIV-1 patients with previous antiretroviral therapy without medical indication for a change of treatment. No data are available for patients with medical changeover indications.

For patients without changeover indication, the ASPIRE and TANGO studies do not show statistically significant differences in the mortality and morbidity categories. No health-related quality of life survey was carried out in the studies. In the side effects category, in the endpoints discontinuation because of AEs, fatigue (PT), and seasonal allergy (PT), statistically significant differences to the detriment of DTG/3TC can be found for this patient group.

The transferability of the results of the patient group without changeover indication to the overall population of therapy experienced adults is unclear. The additional benefit is therefore assessed for the total population of therapy experienced adults. Because the results only apply to a sub-group of this patient group, whose relevance to everyday care is questionable, no additional benefit of DTG/3TC compared with the appropriate comparator therapy can be derived in the overall assessment of the results on mortality, morbidity, and side effects.

c) Therapy naïve adolescent HIV-1 patients above 12 years who have no known or suspected resistance to the integrase inhibitor class or lamivudine

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 DTG/3TC compared with the appropriate comparator therapy.

Overall, an additional benefit of DTG/3TC is therefore not proven for therapy experienced adolescent patients infected with HIV-1.

d) Therapy experienced adolescent HIV-1 patients above 12 years who have no known or suspected resistance to the integrase inhibitor class or lamivudine.

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 DTG/3TC compared with the appropriate comparator therapy.

Overall, an additional benefit of DTG/3TC is therefore not proven for therapy experienced adolescent patients infected with HIV-1.

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

a) Therapy naïve adult HIV-1 patients who have no known or suspected resistance to the integrase inhibitor class or lamivudine

According to the Robert Koch Institute, in Germany, approx. 77,050 patients were diagnosed as infected with HIV at the end of 2018[5]. Approximately 5,650 (7.6%) of the patients diagnosed had not received antiretroviral therapy. Assuming that the number of patients diagnosed for the first time in 2019 corresponds to the number in 2018 (i.e. approx. 2,400), this results in 8,050 therapy naïve patients for the end of 2019. Based on three German cohort studies[6], 0.8% of patients show primary resistance to the nucleoside reverse transcriptase inhibitor (NRTI) lamivudine and are therefore not eligible for the administration of dolutegravir/lamivudine. The number of patients with primary resistance to integrase inhibitors is so small that it is negligible.

Assuming that 88.09% of the German population is covered by statutory health insurance, approx. 7,000 (as mean) therapy naïve adult SHI patients are eligible for the administration of dolutegravir/lamivudine. This represents a concretisation of patient numbers from previous resolutions based on current epidemiological publications.

b) Therapy experienced adult HIV-1 patients who have no known or suspected resistance to the integrase inhibitor class or lamivudine

According to the Robert Koch Institute, in Germany, approx. 71,400 patients had received antiretroviral therapy at the end of 2018[2]. It can be assumed that, according to the figure for 2018, around 2,400 people will become newly infected and 440 will die in 2019. Based on the assumption that antiretrovirally treated patients account for 81.4% of the total number of HIV-infected patients (based on the information provided by the RKI[2]), approx. 2,000 therapy experienced patients are added. The total number of therapy experienced patients should be reduced by the proportion patients with acquired resistance to lamivudine (16.7%) and intergrase inhibitors (6.7%). Because of overlapping of patients with several acquired resistances, the potential resistance situation is unclear; this uncertainty leads to an underestimation of the number of therapy experienced patients.

Assuming that 88.09% of the German population is covered by statutory health insurance, approx. 49,500 (as mean) therapy experience adult SHI patients are eligible for the administration of dolutegravir/lamivudine.

c) Therapy naïve adolescent HIV-1 patients above 12 years who have no known or suspected resistance to the integrase inhibitor class or lamivudine

The pharmaceutical company determines the number of HIV-infected adolescents aged 12 years and older in the target SHI population by querying the cases reported to the RKI in accordance with the Infection Protection Act from the SurvStat@RKI 2.0 database. The pharmaceutical company assumes that all adolescents diagnosed will receive antiretroviral therapy following the diagnosis.

With a SHI proportion of 88.09% and the proportion of patients with resistance to lamivudine (0.8%), this results in about 10 therapy naïve adolescent patients in the target SHI population according to pharmaceutical company.

d) Therapy experienced adolescent HIV-1 patients above 12 years who have no known or suspected resistance to the integrase inhibitor class or lamivudine

Based on a query of the SurvStat@RKI 2.0 database for the diagnosis years 2001 to 2018, the pharmaceutical company determined a number of 174 adolescents who had received antiretroviral treatment. However, this figure also includes adolescents newly diagnosed in 2018 (10 patients) who are considered to be therapy naïve (see above).

[5] Robert Koch Institute – Epidemiological Bulletin 46/2019
[6] Robert Koch Institute – Epidemiological Bulletin 49/2019

If these 10 patients are deducted, taking into account the proportion of patients with acquired resistance to lamivudine and assuming that 88.09% of the German resident population is covered by statutory health insurance, approx. 150–170 therapy experienced adolescent SHI patients are eligible for treatment with dolutegravir/lamivudine. The derivation is subject to various uncertainties, especially because the pharmaceutical company does not take deaths into account and it is assumed that all diagnosed adolescents have been pretreated.

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 Dovato® (active ingredient: dolutegravir/lamivudine at the following publicly accessible link (last access: 22 November 2019):

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

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

2.4 Treatment costs

To calculate the costs of the medicinal products, the required number of packs of a particular potency was first determined on the basis of consumption. The medicinal product costs were calculated with the calculated number of required packs, based on the costs per packs, after deduction of the statutory rebate. 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 and 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 (maraviroc + abacavir + emtricitabine) as an example.

According to the current German guideline[7], 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 January 2020).

Because in the present case the G-BA assessed only the question of the additional benefit of a two-fold combination, only this combination is taken into account for the cost representation.

[7] German-Austrian guidelines for antiretroviral therapy of HIV infection (consented Version 2019)

Treatment duration:

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

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

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Emtricitabine/tenofovir alafenamide	continuously, 1 × daily	365	1	365
Dolutegravir/abacavir/lamivudine				
Dolutegravir/abacavir/lamivudine	continuously, 1 × daily	365	1	365
Patient population d)				
Nevirapine + emtricitabine/tenofovir disoproxil				
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	Dosage/ patient/treatment days	Consumption by potency/treatment day	Treatment days/patient year	Annual average consumption by potency
Medicinal product to be assessed					
Dolutegravir/lamivudine	50 mg/300 mg	50 mg/300 mg	1 × 50 mg/300 mg	365	365 × 50 mg/300 mg
Appropriate comparator therapy					
Patient population a)					
Rilpivirine + tenofovir disoproxil/emtricitabine					

Rilpivirine Emtricitabine/tenofovir disoproxil	25 mg 200 mg/245 mg	25 mg 200 mg/245 mg	1 × 25 mg 1 × 200 mg/245 mg	365 365	365 × 25 mg 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 600 mg/300mg	25 mg 600 mg/300 mg	1 × 25 mg 1 × 600 mg/300 mg	365 365	365 × 25 mg 365 × 600 mg/300 mg
Dolutegravir + tenofovir disoproxil/emtricitabine					
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 Emtricitabine/tenofovir disoproxil	200 mg 200 mg/245 mg	400 mg 200 mg/245 mg	2 × 200 mg 1 × 200 mg/245 mg	365 365	730 × 200 mg 365 × 200 mg/245 mg

Maraviroc + abacavir + emtricitabine					
Maraviroc Abacavir Emtricitabine	300 mg 300 mg 200 mg	600 mg 600 mg 200 mg	2 × 300 mg 2 × 300 mg 1 × 200 mg	365 365 365	730 × 300 mg 730 × 300 mg 365 × 200 mg
Patient population c)					
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 600 mg/300mg	25 mg 600 mg/300 mg	1 × 25 mg 1 × 600 mg/300 mg	365 365	365 × 25 mg 365 × 600 mg/300 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 d)					
Nevirapine + emtricitabine/tenofovir disoproxil					
Nevirapine Emtricitabine/tenofovir disoproxil	200 mg 200 mg/245 mg	400 mg 200 mg/245 mg	2 × 200 mg 1 × 200 mg/245 mg	365 365	730 × 200 mg 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					
Dolutegravir/lamivudine	90 FCT	€ 2,518.74	€ 1.77	€ 140.57	€ 2,376.40
Appropriate comparator therapy					
Patient population a) + c)					
Abacavir/lamivudine	30 FCT	€ 467.67	€ 1.77	€ 21.67	€ 444.23
Dolutegravir/abacavir/lamivudine	90 FCT	€ 2,925.52	€ 1.77	€ 0.00	€ 2,923.75
Dolutegravir	90 FCT	€ 2,134.94	€ 1.77	€ 0.00	€ 2,133.17
Emtricitabine/tenofovir disoproxil	60 FCT	€ 96.06	€ 1.77	€ 4.03	€ 90.26
Emtricitabine/tenofovir alafenamide	90 FCT	€ 1,528.22	€ 1.77	€ 84.00	€ 1,442.45
Rilpivirine	30 FCT	€ 374.28	€ 1.77	€ 0.00	€ 372.51
Patient population b) + d)					
Abacavir 300 mg	60 FCT	€ 348.61	€ 1.77	€ 16.02	€ 330.82
Emtricitabine	30 HC	€ 302.47	€ 1.77	€ 16.14	€ 284.56
Emtricitabine/tenofovir disoproxil	60 FCT	€ 96.06	€ 1.77	€ 4.03	€ 90.26
Maraviroc	60 FCT	€ 1,073.06	€ 1.77	€ 58.80	€ 1,012.49
Nevirapine	120 TAB	€ 267.57	€ 1.77	€ 13.23	€ 252.57
Abbreviations: FCT = film-coated tablets, HC = hard capsules, TAB = tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 January 2020

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

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 29 January 2019.

On 3 July 2019, the pharmaceutical company submitted a dossier for the benefit assessment of dolutegravir/lamivudine to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 4 July 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 dolutegravir/lamivudine.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 October 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 November 2019. The deadline for submitting written statements was 22 November 2019.

The oral hearing was held on 9 December 2019.

By letter dated 9 December 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The two addenda prepared by IQWiG were submitted to the G-BA on 16 January 2020 and on 22 January 2020.

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 were discussed at the session of the subcommittee on 28 January 2020, and the proposed resolution was approved.

At its session on 6 February 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	29 January 2019	Determination of the appropriate comparator therapy
Working group Section 35a	3 December 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	9 December 2019	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 December 2019 21 January 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	28 January 2020	Concluding consultation of the proposed resolution
Plenum	6 February 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 6 February 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken