Gemeinsamer Bundesausschuss

Justification

for the Resolution of the Federal Joint Committee (G-BA) on a non-amendment of the Pharmaceuticals Directive Annex XII - Procedure for initiating a new benefit assessment according to Section 35a paragraph 1 SGB V in conjunction with Section 3 paragraph 1 No. 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) and Chapter 5 Section 13 Rules of Procedure (VerfO) – Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

Dolutegravir

of 15 September 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

2. Key points of the resolution

The active ingredient dolutegravir (Tivicay) was first marketed on 15 February 2014. By resolution of 20 August 2020, last amended on 2 December 2021 (Federal Gazette, BAnz AT 17.12.2021 B8), the G-BA, at the request of its members, initiated a new benefit assessment according to Section 35a paragraph 1 SGB V in conjunction with Section 3, paragraph 1, No. 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) and Chapter 5 Section 13 of the Rules of Procedure (VerfO) for the active ingredient dolutegravir. The new benefit assessment was initiated by new scientific findings from the ODYSSEY (NCT02259127) study.

The legal reason for initiating a new benefit assessment for the active ingredient dolutegravir was that the data of the ODYSSEY study are to be regarded as new scientific findings that fulfil the criteria for a new benefit assessment to be initiated ex officio by the G-BA due to new scientific findings according to Section 35a paragraph 1 SGB V in conjunction with Section 3, paragraph 1, No. 4 AM-NutzenV and Chapter 5, Section 13, paragraph 4 VerfO. Due to the direct comparator of a dolutegravir-containing regimen versus standard of care in children and adolescents with HIV infection aged 6 to < 18 years and the collection of patient-relevant endpoints, such as virological response, CD4+ cell count and AIDS-defining events, in a therapeutic indication with limited comparative evidence, the ODYSSEY study was estimated to be relevant for a new benefit assessment due to new scientific findings.

In view of the limited comparative evidence in the therapeutic indication, the significance of the ODYSSEY study was therefore assessed as high and the resulting findings obtained were considered fundamentally relevant for the German healthcare context.

According to the pharmaceutical company, the sponsor of the ODYSSEY study is the Paediatric European Network for Treatment of Acquired Immunodeficiency Syndrome Foundation (PENTA Foundation).

The relevant date for the active ingredient dolutegravir in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO is 1 April 2022. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 4 AM-NutzenV in conjunction with Chapter 5, Section 8, paragraph 1, number 6 VerfO on 30 March 2022.

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 1 July 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

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

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

The pharmaceutical company submitted the dossier for the assessment of the additional benefit of dolutegravir in combination with other antiretrovirals compared to the appropriate comparator therapy but the data were not assessable for any of the specific patient groups.

By resolution of 20 August 2020, last amended on 2 December 2021 (Federal Gazette, BAnz AT 17.12.2021 B8), the G-BA initiated the new benefit assessment of dolutegravir on the basis of new scientific findings in the treatment of a HIV infection in children and adolescents aged 6 to < 18 years, taking into account the ODYSSEY study.

The ODYSSEY study is a multicentre, open-label, randomised controlled trial comparing antiretroviral therapy (ART) consisting of dolutegravir and two nucleoside or nucleotide reverse transcriptase inhibitors (NRTI) versus standard of care (SOC) therapy. This SOC was composed of a non-dolutegravir-based ART of two NRTIs and a boosted protease inhibitor or a non-nucleoside reverse transcriptase inhibitor or another integrase inhibitor.

Children and adolescents aged < 18 years with HIV-1 infection without integrase inhibitor resistance with a body weight ≥ 14 kg were enrolled in the study and randomised to two cohorts. Cohort A included 311 therapy naïve children and adolescents and cohort B included 396 pretreated children and adolescents for whom second-line ART was indicated due to therapy failure.

The primary endpoint of the study was virological or clinical therapy failure, and additional endpoints collected were mortality, morbidity, health-related quality of life, health status and adverse events (AEs).

The median observation period in the study was 142 weeks.

The following information on the ODYSSEY study was obtained from IQWiG's dossier assessment (A22-38), which was published on the G-BA website on 1 July 2022:

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

On therapy naive patients

Cohort A of the ODYSSEY study includes therapy naïve children and adolescents aged < 18 years with HIV-1 infection without integrase inhibitor resistance with a body weight ≥ 14 kg.

For therapy naïve children with HIV aged 6 to < 12 years who have no known or suspected resistance to the class of integrase inhibitors, dolutegravir in combination with other antiretrovirals atazanavir plus ritonavir in combination with abacavir plus emtricitabine, or in combination with abacavir plus lamivudine was determined as the appropriate comparator therapy.

For therapy naïve adolescents with HIV aged 12 to < 18 years who have no known or suspected resistance to the class of integrase inhibitors, rilpivirine plus tenofovir alafenamide plus emtricitabine, or in combination with abacavir plus lamivudine was determined as the appropriate comparator therapy for dolutegravir in combination with other antiretrovirals.

In the ODYSSEY study, 145 of 157 (92%) therapy naïve children and adolescents in the control arm received an efavirenz-based ART.

Treatment with efavirenz-containing treatment regimens does not correspond to an adequate implementation of the G-BA-determined appropriate comparator therapy for therapy naïve children and adolescents with HIV infection.

With a large proportion of the therapy naïve children and adolescents in the ODYSSEY study being treated with efavirenz-containing treatment regimens, the study is not suitable for the benefit assessment for this patient group, as the appropriate comparator therapy was not implemented.

On therapy experienced patients

Cohort B of the ODYSSEY study includes therapy experienced children and adolescents aged < 18 years with HIV-1 infection without integrase inhibitor resistance with a body weight ≥ 14 kg for whom second-line ART was indicated due to therapy failure.

In the course of the study, the doses of dolutegravir were adjusted in the product information. According to the current product information, children with a body weight of 14 to < 20 kg are treated with 40 mg dolutegravir and children and adolescents with a body weight of 20 kg or more are usually treated with 50 mg dolutegravir once daily.

Due to the change in dosing in the product information, the dosage of dolutegravir (DTG) was adjusted accordingly in the intervention arm of the ODYSSEY study. The adjustments are shown by body weight in the following table:

Body weight	**Dosage DTG at the start of the study**	**Dosage DTG from May 2018**	**Dosage DTG from May 2019**
14 to < 20 kg	20 mg	25 mg	25 mg
20 to < 25 kg	25 mg	25 or 30 or 50 mg	50 mg
25 to < 30 kg	25 mg	25 or 50 mg	50 mg
30 to < 40 kg	35 mg	35 or 50 mg	50 mg
above 40 kg	50 mg	50 mg	50 mg

Accordingly, in the ODYSSEY study, only children and adolescents weighing 40 kg and above were dosed from the beginning according to the current marketing authorisation. For children and adolescents with a body weight of 20 to < 40 kg, dosage was possible according to the current marketing authorisation from May 2018, but the percentage of this sub-population

cannot be conclusively assessed. Therefore, only a sub-population of unknown size from the ODYSSEY study corresponds to the approved therapeutic indication.

The pharmaceutical company does not use the ODYSSEY study for the benefit assessment due to the substantial part of the relevant study population that has not been treated according to the current dolutegravir product information.

Conclusion

The ODYSSEY study is a randomised controlled trial conducted in children and adolescents aged < 18 years, which for the first time generates direct comparative evidence in the present therapeutic indication of HIV infection in this age group.

Endpoints on morbidity such as virologic failure or response and AIDS-defining events (WHO grade 3 and 4), health-related quality of life and side effects were collected. The results of such endpoints assessed as patient-relevant compared to non-dolutegravir-based ART are basically assessed as new scientific findings.

However, the ODYSSEY study is not suitable for the derivation of an additional benefit due to the lack of implementation of the appropriate comparator therapy in therapy naïve children and adolescents and the dosage of dolutegravir in therapy experienced children and adolescents, which was partly not in line with the product information, as determined by the IQWiG.

Even though the ODYSSEY study leads to new scientific findings for children and adolescents with HIV aged 6 to < 18 years, the results of the study are not considered to be new evidence in the present therapeutic indication due to the lack of suitability of the study identified in IQWiG's review. For this reason, the resolutions on dolutegravir of 7 August 2014 (Federal Gazette, BAnz AT 07.10.2014 B2) and of 21 September 2017 (Federal Gazette, BAnz AT 19.10.2017 B3) on the amendment to Annex XII of the Pharmaceuticals Directive continue to be assessed as reflecting the available evidence and remain valid. An amendment to Annex XII of the Pharmaceuticals Directive due to the initiation of a new benefit assessment according to Section 35a paragraph 1 SGB V in conjunction with Section 3, paragraph 1, No. 4 AM-NutzenV and Chapter 5 Section 13 VerfO: Annex XII – Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V on the active ingredient dolutegravir by resolution of 20 August 2020, last amended on 2 December 2021 (Federal Gazette, BAnz AT 17.12.2021 B8), is therefore not carried out.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 10 August 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 March 2022, the pharmaceutical company submitted a dossier for the benefit assessment of dolutegravir to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO.

By letter dated 1 April 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient dolutegravir.

The dossier assessment by the IQWiG was submitted to the G-BA on 23 June 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2022. The deadline for submitting written statements was 22 July 2022.

The oral hearing was held on 8 August 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 6 September 2022, and the proposed resolution was approved.

At its session on 15 September 2022, the plenum adopted this resolution.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 August 2021	Determination of the appropriate comparator therapy
Working group Section 35a	3 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2022	Conduct of the oral hearing,
Working group Section 35a	17 August 2022 31 August 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 September 2022	Concluding discussion of the draft resolution
Plenum	15 September 2022	Resolution

Berlin, 15 September 2022

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

Prof. Hecken