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Dolutegravir (HIV infection in children) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dolutegravir. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 February 2021.

Research question

The aim of the present report is to assess the added benefit of dolutegravir in comparison with the appropriate comparator therapy (ACT) in children with human immunodeficiency virus (HIV) infection aged ≥ 4 weeks to < 6 years who weigh at least 3 kg.

The research questions presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of dolutegravir

Research question	Therapeutic indication	ACT[a]
1	Treatment-naive children with HIV-1 infection aged ≥ 4 weeks to < 6 years[b]	Abacavir with lamivudine or abacavir with emtricitabine, each in combination with ▪ lopinavir/ritonavir or ▪ raltegravir or ▪ nevirapine
2	Treatment-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years[b]	Individual antiretroviral therapy chosen from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects

a. Presentation of the respective ACT specified by the G-BA.
b. With a body weight of at least 3 kg.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1

The company followed the specification of the ACT for both research questions. Deviating from the G-BA, the company did not differentiate between the populations of treatment-naive and treatment-experienced children. Concurring with the G-BA's specification, the present assessment was conducted for both research questions 1 and 2.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 48 weeks were used for the derivation of the added benefit.

Results

Concurring with the company, the check of the completeness of the study pool identified no study for the direct comparison of dolutegravir with the ACT in the present therapeutic indication. Results for the company's ongoing RCT ODYSSEY in the therapeutic indication are presently not available.

As there are no RCTs with available data, the company conducted an information retrieval for non-randomized comparative studies and other investigations. It identified two single-arm studies on dolutegravir (IMPAACT P1093 and ODYSSEY WB-PK1/2) as further studies. The company conducted no information retrieval of further investigations with the ACT.

Due to the lack of a comparison with the ACT, the further investigations presented by the company were unsuitable for deriving an added benefit of dolutegravir. This is explained below.

Data presented by the company

Study IMPAACT P1093

IMPAACT P1093 is a single-arm, multicentre, open-label study with dolutegravir in HIV-1 infected children and adolescents aged ≥ 4 weeks to < 18 years with a body weight of at least 3 kg. The study included both treatment-naive patients and patients who had already received antiretroviral therapy (ART).

Study ODYSSEY WB-PK1/2

ODYSSEY WB-PK1/2 is a pharmacokinetics substudy of the ODYSSEY study. ODYSSEY is a randomized, multicentre, open-label non-inferiority study for the comparison of dolutegravir in combination with an antiretroviral background therapy with the standard therapy in HIV-1 infected children and adolescents aged ≥ 28 days to < 18 years with a body weight of at least 3 kg. The study included both treatment-naive and ART-experienced patients. The pharmacokinetics substudy ODYSSEY WB-PK1/2 included patients with a body weight of ≥ 3 kg to < 40 kg from the dolutegravir arm of the ODYSSEY study. Thus, the ODYSSEY WB-PK1/2 substudy is a single-arm study with dolutegravir.

The data presented are unsuitable for deriving an added benefit

The company provided a descriptive presentation of the results of the relevant subpopulation from the two single-arm studies on dolutegravir without differentiating by pretreatment status in accordance with the research question. It presented no data on the ACT and made no comparison with the ACT.

Based on the non-comparative data on dolutegravir, the company derived a hint of a non-quantifiable added benefit. This was justified with a high antiretroviral efficacy, a good tolerability and the advantage of the age-appropriate administration of dolutegravir.

The approach of the company to derive an added benefit on the basis of the single-arm studies on dolutegravir was not appropriate, since data for a comparison with the respective ACT were not available for any of the research questions.

The company itself conducted no comparison at all with the ACT. In its argumentation on the added benefit, it cited, among other things, the high antiretroviral efficacy of dolutegravir. However, based on an exemplary comparison with published data, this efficacy ranges in a magnitude that seems possible also for the ACT.

In its dossier, the company therefore presented no suitable data to assess the added benefit of dolutegravir in treatment-naive and treatment-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years compared with the ACT defined by the G-BA for each of the 2 research questions. In each case, this resulted in no hint of an added benefit of dolutegravir in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of dolutegravir.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Dolutegravir – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment-naive children with HIV-1 infection aged ≥ 4 weeks to < 6 years[b]	Abacavir with lamivudine or abacavir with emtricitabine, each in combination with ▪ lopinavir/ritonavir or ▪ raltegravir or ▪ nevirapine	Added benefit not proven
Treatment-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years[b]	Individual antiretroviral therapy chosen from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. With a body weight of at least 3 kg.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of dolutegravir in comparison with the ACT in children with HIV infection aged ≥ 4 weeks to < 6 years who weigh at least 3 kg.

The research questions presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of dolutegravir

Research question	Therapeutic indication	ACT[a]
1	Treatment-naive children with HIV-1 infection aged ≥ 4 weeks to < 6 years[b]	Abacavir with lamivudine or abacavir with emtricitabine, each in combination with ▪ lopinavir/ritonavir or ▪ raltegravir or ▪ nevirapine
2	Treatment-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years[b]	Individual antiretroviral therapy chosen from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects

a. Presentation of the respective ACT specified by the G-BA.
b. With a body weight of at least 3 kg.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1

The company followed the specification of the ACT for both research questions. Deviating from the G-BA, the company did not differentiate between the populations of treatment-naive and treatment-experienced children. Concurring with the G-BA's specification, the present assessment was conducted for both research questions 1 and 2.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 48 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on dolutegravir (status: 1 December 2020)
- bibliographical literature search on dolutegravir (last search on 1 December 2020)
- search in trial registries/trial results databases for studies on dolutegravir (last search on 1 December 2020)
- search on the G-BA website for dolutegravir (last search on 1 December 2020)

To check the completeness of the study pool:

- search in trial registries for studies on dolutegravir (last search on 10 February 2021)

Concurring with the company, the check of the completeness of the study pool identified no study for the direct comparison of dolutegravir with the ACT in the present therapeutic indication. Results for the ongoing RCT ODYSSEY [3] in the therapeutic indication are presently not available.

As there are no RCTs with available data, the company conducted an information retrieval for non-randomized comparative studies and other investigations. As further investigations, it thereby identified two single-arm studies on dolutegravir (IMPAACT P1093 [4] und ODYSSEY WB-PK1/2 [5]). The company conducted no information retrieval of further investigations with the ACT.

A check of the completeness of the study pool presented by the company for the further investigations was not performed, as the further investigations submitted by the company were not suitable for deriving an added benefit of dolutegravir due to the lack of comparison with the ACT. This is explained below.

Data presented by the company

Under "Further investigations", the company presented data on the following single-arm studies in the dossier for which the company was not the sponsor and on the basis of which the approval was extended.

Study IMPAACT P1093

IMPAACT P1093 is a single-arm, multicentre, open-label study with dolutegravir in HIV-1 infected children and adolescents aged ≥ 4 weeks to < 18 years with a body weight of at least 3 kg. The study included both treatment-naive patients and patients who had already received ART.

In Module 4 A of the dossier, the company presented data on a subpopulation of 51 children in whom age (≥ 4 weeks to < 6 years) and pharmaceutical form of dolutegravir (tablet for the preparation of a suspension for oral use) used corresponded to the present therapeutic indication. 86.3% of them were pre-treated with ART. According to the Summary of Product Characteristics (SPC), dolutegravir was administered in combination with an optimized antiretroviral background therapy depending on body weight and age [6]. The dose of dolutegravir used in the IMPAACT P1093 study for children older than 6 months and weighing less than 6 kg deviates from the specifications of the SPC. However, it is unclear how many children were affected by this deviation. Module 4 A of the dossier only provides information on the drug classes used for the optimized antiretroviral background therapy, which according to the guideline is to be selected for the individual patient under consideration of resistances, among other things [7]. Specific information on the drugs used and on resistances at baseline is not available.

Primary outcome of the study was "adverse events (AEs)" until week 24. Secondary patient-relevant outcomes were "AEs until week 48". The study is ongoing and the treatment duration is 48 weeks.

Study ODYSSEY WB-PK1/2

ODYSSEY WB-PK1/2 is a pharmacokinetics substudy of the ODYSSEY study. ODYSSEY is a randomized, multicentre, open-label non-inferiority study for the comparison of dolutegravir in combination with an antiretroviral background therapy with the standard therapy in HIV-1 infected children and adolescents aged ≥ 28 days to < 18 years with a body weight of at least 3 kg. Both treatment-naive and ART-experienced patients were included (see also the following Section "Potentially relevant data from the ODYSSEY study"). The pharmacokinetics substudy ODYSSEY WB-PK1/2 included patients with a body weight of ≥ 3 kg to < 40 kg from the dolutegravir arm of the ODYSSEY study. Thus, the ODYSSEY WB-PK1/2 substudy is a single-arm study with dolutegravir.

In Module 4 A of the dossier, the company presented data on a subpopulation of 16 children in whom age (≥ 4 weeks to < 6 years) and pharmaceutical form of dolutegravir (tablet for the preparation of a suspension for oral use) used corresponded to the present therapeutic indication. 81.3% of them were treatment-naive. According to the SPC, dolutegravir was administered in combination with an optimized antiretroviral background therapy depending on body weight and age [6]. Module 4 A of the dossier only provides information on the drug classes used for the optimized antiretroviral background therapy, which according to the guideline is to be selected for the individual patient under consideration of resistances, among other things [7]. Information on the drugs used and on resistances at baseline is not available.

The primary outcome was "pharmacokinetics". Patient-relevant secondary outcomes were AEs. The treatment duration is 96 weeks.

Potentially relevant data from the ODYSSEY study

For the currently still ongoing RCT ODYSSEY on the comparison of dolutegravir in combination with antiretroviral background therapy versus the standard therapy, the standard therapy is described as ART consisting of a boosted protease inhibitor, a non-nucleoside reverse transcriptase inhibitor or an integrase inhibitor, each in combination with nucleoside reverse transcriptase inhibitors. The respective individual treatment was determined before randomization [3,8]. Based on the information hitherto available, the ODYSSEY study was assessed as potentially relevant for the present therapeutic indication. First data from this study are expected by the end of 2021 and a manuscript will be submitted to the European Medicines Agency (EMA) [3,9].

Approach of the company

The company provided a descriptive presentation of the results of the relevant subpopulations from the two single-arm studies on dolutegravir without differentiating by pretreatment status in accordance with the research question. Data on efficacy and safety are available from

IMPAACT P1093; from the ODYSSEY WB-PK1/2 study, there are only safety data. The company presented no data on the ACT and made no comparison with the ACT.

Based on the non-comparative data on dolutegravir, the company derived a hint of a non-quantifiable added benefit. This was justified with a high antiretroviral efficacy, a good tolerability and the advantage of the age-appropriate administration of dolutegravir.

The data presented are unsuitable for deriving an added benefit

The approach of the company to derive an added benefit on the basis of the single-arm studies on dolutegravir described in the previous section was not appropriate, since data for a comparison with the respective ACT were not available for any of the research questions. There are thus no suitable data for the assessment of the added benefit of dolutegravir in the therapeutic indication.

The company itself conducted no comparison at all with the ACT. In its argumentation on the added benefit, it cited, among other things, the high antiretroviral efficacy of dolutegravir. However, based on an exemplary comparison with published data, this efficacy ranges in a magnitude that seems possible [10] also for the ACT.

2.4 Results on added benefit

In its dossier, the company thus presented no suitable data to assess the added benefit of dolutegravir in treatment-naive and treatment-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years compared with the ACT defined by the G-BA for each of the 2 research questions. In each case, this resulted in no hint of an added benefit of dolutegravir in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of dolutegravir in comparison with the ACT is summarized in Table 5.

Table 5: Dolutegravir – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment-naive children with HIV-1 infection aged ≥ 4 weeks to < 6 years[b]	Abacavir with lamivudine or abacavir with emtricitabine, each in combination with ▪ lopinavir/ritonavir or ▪ raltegravir or ▪ nevirapine	Added benefit not proven
Treatment-experienced children with HIV-1 infection aged ≥ 4 weeks to < 6 years[b]	Individual antiretroviral therapy chosen from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. With a body weight of at least 3 kg.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1

The assessment described above deviates from that of the company, which presented the data without differentiating by pretreatment status and derived a hint of non-quantifiable added benefit based on these non-comparative data.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a21-14.html.