

IQWiG Reports – Commission No. A17-11

# **Dolutegravir (HIV infection) –**

## **Benefit assessment according to §35a Social Code Book V<sup>1</sup>**

**Extract**

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<sup>1</sup> Translation of Sections 2.1 to 2.5 of the dossier assessment *Dolutegravir (HIV-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 June 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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<sup>3</sup> Table numbers start with “2” as numbering follows that of the full dossier assessment.

**List of abbreviations**

<b>Abbreviation</b>	<b>Meaning</b>
ACT	appropriate comparator therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
CD4	cluster of differentiation 4
DAIDS	Division of AIDS
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)
NRTI	nucleoside reverse transcriptase inhibitor
RCT	randomized controlled trial
RNA	ribonucleic acid
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 17 March 2017.

#### Research question

The aim of this report was to assess the added benefit of dolutegravir in comparison with the appropriate comparator therapy (ACT) in children from  $\geq 6$  to  $< 12$  years of age infected with the human immunodeficiency virus (HIV).

The G-BA’s specification of the ACT resulted in the following 2 research questions for the benefit assessment:

Table 2: Research questions of the benefit assessment of dolutegravir

Research question	Subindication	ACT <sup>a</sup>
1	Treatment-naïve children from $\geq 6$ to $< 12$ years of age	ART consisting of 2 NRTIs (abacavir or lamivudine or emtricitabine or zidovudine) and 1 NNRTI (efavirenz or nevirapine) or 1 protease inhibitor (lopinavir or atazanavir or darunavir, each in combination with ritonavir)
2	ART-experienced children from $\geq 6$ to $< 12$ years of age	Individual ART based on prior treatment(s) and under consideration of 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.  
 ACT: appropriate comparator therapy; ART: antiretroviral therapy; G-BA: Federal Joint Committee;  
 NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

#### Results

##### *Research question 1: treatment-naïve children from $\geq 6$ to $< 12$ years of age*

To derive the added benefit, the company tried to transfer the results of 2 dolutegravir studies conducted in treatment-naïve adults, SPRING-1 and SINGLE, to the target population of children. The studies SPRING-1 and SINGLE were already known from a previous benefit assessment of dolutegravir in adults. The company’s approach to transfer study results for adults to children is understandable because there were no comparative data for children. The

concrete implementation was inadequate, however. Hence no added benefit of dolutegravir in comparison with the ACT in children can be derived:

- The company did not present any data for treatment-naïve children in the therapeutic indication.
- In addition, the company used only those randomized controlled trials (RCTs) for adults that had already been included in the first assessment of dolutegravir (A14-08). In these RCTs, the patients in the comparator arms were treated with the ACT specified for treatment-naïve adults. However, this ACT does not concur with the ACT specified for children. Hence, the company did also not present any analyses for adults on the comparison of dolutegravir with the ACT relevant for children.
- In addition, the data presented by the company were incomplete. For example, the check of completeness revealed 1 RCT conducted by the company itself in treatment-naïve adults on the comparison of dolutegravir with darunavir/ritonavir, each in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir + lamivudine or emtricitabine + tenofovir). Some patients in this study were treated with an ACT option for children. This study was not considered by the company, however.

In summary, an added benefit is not proven for this research question.

***Research question 2: pretreated children from  $\geq 6$  to  $< 12$  years of age***

To derive the added benefit, the company tried to transfer the results of the dolutegravir study SAILING conducted in pretreated adults to the target population of children from  $\geq 6$  to  $< 12$  years of age. The SAILING study was already known from a previous benefit assessment of dolutegravir in adults.

In order to transfer the results, the company additionally used the findings of a single-arm study on dolutegravir, which was conducted in children and adolescents (study IMPAACT [P0193]). This study included a total of 23 patients in the population relevant for the therapeutic indication, i. e. children from  $\geq 6$  to  $< 12$  years of age. The mean age at study inclusion was 9 years.

The company's approach to transfer study results for adults to children is understandable because there were no comparative data for children. However, the concrete implementation by the company was insufficient for various reasons. No added benefit of dolutegravir in comparison with the ACT in pretreated children from  $\geq 6$  to  $< 12$  years of age could be derived from the company's approach. The following aspects in particular were decisive for this:



- The ACT specified by the G-BA in the therapeutic indication of children from  $\geq 6$  to  $< 12$  years of age was not investigated at all. The company conducted no information retrieval for the ACT for further investigations. As a result, a single-arm study with raltegravir in pretreated children was not considered, for example.
- The data of the single-arm study IMPAACT presented in the therapeutic indication for children were incomplete. There was no presentation of all relevant outcomes at week 48, which is also required for a comparison with the 48-week results of the SAILING study in adults.
- The dossier contained no comparison of the patient characteristics or of the results of patient-relevant outcomes between the single-arm study IMPAACT in children and the RCT SAILING in adults. Correspondingly, there was no critical investigation of the differences observed between children and adults. Such an investigation of the studies presented by the company would provide a reason against transferability of the study results to children:
  - The patient characteristics of the children in the IMPAACT study partly differed markedly from those of the adults in the SAILING study regarding ethnicity and disease severity.
  - The data presented did not support transferability of the treatment effects from the first assessment A14-08 in adults. For example, there was a notable difference between the IMPAACT study and the dolutegravir arm of the SAILING study for the results for the outcome “severe adverse events (AEs)” grade 3–4 (Division of acquired immunodeficiency syndrome [AIDS] [DAIDS]).
- The company did not show that integrase inhibitors were the first treatment option in the sense of individual antiretroviral therapy for the children in the IMPAACT study. The G-BA had determined an added benefit of dolutegravir on the basis of the SAILING study only for this subpopulation of pretreated patients.

In summary, an added benefit is not proven for this research question.

### **Probability and extent of added benefit, patient groups with therapeutically important added benefit<sup>4</sup>**

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

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<sup>4</sup> 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, no added benefit, or less benefit). For further details see [1,2].

Table 3: Dolutegravir – probability and extent of added benefit

Research question	Subindication	ACT <sup>a</sup>	Probability and extent of added benefit
1	Treatment-naive children from $\geq 6$ to $< 12$ years of age	ART consisting of 2 NRTIs (abacavir or lamivudine or emtricitabine or zidovudine) and 1 NNRTI (efavirenz or nevirapine) or 1 protease inhibitor (lopinavir or atazanavir or darunavir, each in combination with ritonavir)	Added benefit not proven
2	ART-experienced children from $\geq 6$ to $< 12$ years of age	Individual ART based on prior treatment(s) and under consideration of 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.  
 ACT: appropriate comparator therapy; ART: antiretroviral therapy; G-BA: Federal Joint Committee;  
 NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor

The G-BA decides on the added benefit.

## 2.2 Research question

The aim of this report was to assess the added benefit of dolutegravir in comparison with the ACT in children from  $\geq 6$  to  $< 12$  years of age infected with HIV.

The G-BA's specification of the ACT resulted in the following 2 research questions for the benefit assessment:

Table 4: Research questions of the benefit assessment of dolutegravir

Research question	Subindication	ACT <sup>a</sup>
1	Treatment-naïve children from $\geq 6$ to $< 12$ years of age	ART consisting of 2 NRTIs (abacavir or lamivudine or emtricitabine or zidovudine) and 1 NNRTI (efavirenz or nevirapine) or 1 protease inhibitor (lopinavir or atazanavir or darunavir, each in combination with ritonavir)
2	ART-experienced children from $\geq 6$ to $< 12$ years of age	Individual ART based on prior treatment(s) and under consideration of 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.  
 ACT: appropriate comparator therapy; ART: antiretroviral therapy; G-BA: Federal Joint Committee;  
 NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

## 2.3 Research question 1: treatment-naïve children from $\geq 6$ to $< 12$ years of age

### 2.3.1 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 lists on dolutegravir (status: 20 December 2016)
- bibliographical literature search on dolutegravir (last search on 20 December 2016)
- search in trial registries for studies on dolutegravir (last search on 20 December 2016)

To check the completeness of the study pool:

- search in trial registries for studies on dolutegravir (last search on 7 April 2017)

Concurring with the company, the check of the completeness of the study pool did not produce any RCTs with the paediatric target population (children from  $\geq 6$  to  $< 12$  years of

age) on the direct comparison of dolutegravir versus the ACT or on a corresponding indirect comparison based on RCTs.

To derive the added benefit, the company tried to transfer the results of 2 dolutegravir studies conducted in treatment-naive adults, SPRING-1 and SINGLE, to the target population of children. The studies SPRING-1 and SINGLE were already known from a previous benefit assessment of dolutegravir in adults [3-5] (see also Section 2.6.2.3.2 of the full dossier assessment). The company's approach to transfer study results for adults to children is understandable because there were no comparative data for children. The concrete implementation was inadequate, however:

- The company did not present any data for treatment-naive children in the therapeutic indication.
- In addition, the company used only those RCTs for adults that had already been included in the first assessment of dolutegravir (A14-08). In these RCTs, the patients in the comparator arms were treated with the ACT specified for treatment-naive adults [3,4]. However, this ACT does not concur with the ACT specified for children. Hence, the company did also not present any analyses for adults on the comparison of dolutegravir with the ACT relevant for children. The company therefore also disregarded the G-BA's consultation. According to the written record of this consultation, the G-BA recommended using studies that were conducted with the ACT specified for children [6] when transferring results for adults to the patient group of children.
- In addition, the data presented by the company were incomplete. For example, the check of completeness revealed 1 RCT conducted by the company itself in treatment-naive adults on the comparison of dolutegravir with darunavir/ritonavir, each in combination with 2 NRTIs (abacavir + lamivudine or emtricitabine + tenofovir) [7]. Some patients in this study were treated with an ACT option for children. This study was not considered by the company, however.

### **2.3.2 Results on added benefit**

In its dossier, the company did not present any suitable data for the assessment of the added benefit of dolutegravir versus the ACT in treatment-naive children from  $\geq 6$  to  $< 12$  years of age. This resulted in no hint of an added benefit of dolutegravir in comparison with the ACT; an added benefit is therefore not proven.

### **2.3.3 Probability and extent of added benefit**

Since the company did not present any suitable data for the assessment of the added benefit of dolutegravir in comparison with the ACT in treatment-naive HIV-infected children from  $\geq 6$  to  $< 12$  years of age, an added benefit of dolutegravir is not proven for these patients.

#### **2.3.4 List of included studies**

Not applicable as the company presented no relevant data for the benefit assessment.

### **2.4 Research question 2: pretreated children from $\geq 6$ to $< 12$ years of age**

#### **2.4.1 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 lists on dolutegravir (status: 20 December 2016)
- bibliographical literature search on dolutegravir (last search on 20 December 2016)
- search in trial registries for studies on dolutegravir (last search on 20 December 2016)

To check the completeness of the study pool:

- search in trial registries for studies on dolutegravir (last search on 7 April 2017)

Concurring with the company, the check of the completeness of the study pool did not produce any RCTs with the paediatric target population on the direct comparison of dolutegravir versus the ACT or on a corresponding indirect comparison based on RCTs.

To derive the added benefit, the company tried to transfer the results of the dolutegravir study SAILING conducted in pretreated adults to the target population of children from  $\geq 6$  to  $< 12$  years of age. The SAILING study was already known from a previous benefit assessment of dolutegravir in adults [3-5]. In order to transfer the results, the company additionally used the findings of a single-arm study on dolutegravir, which was conducted in children and adolescents (study IMPAACT [P0193] [8-10]). The company additionally presented results of the open-label RCT OSTEODOLU [11,12] (see Section 2.6.2.3.2 of the full dossier assessment).

The company's approach to transfer study results for adults to children is understandable because there were no comparative data for children. However, the concrete implementation by the company was insufficient for various reasons. No added benefit of dolutegravir in comparison with the ACT in pretreated children from  $\geq 6$  to  $< 12$  years of age could be derived from the company's approach. This is justified below.

#### **Single-arm dolutegravir study (IMPAACT)**

The IMPAACT study was a single-arm, open-label study with dolutegravir in ART-experienced HIV-1-infected children and adolescents from  $\geq 4$  weeks to  $< 18$  years of age. This study included a total of 23 patients in the population relevant for the therapeutic indication, i. e. children from  $\geq 6$  to  $< 12$  years of age. Dolutegravir was administered once daily orally in addition to an individually optimized antiretroviral background therapy, in

compliance with the specifications of the Summary of Product Characteristics (SPC) [13]. Mean age at study inclusion was 9 years, 17% of the children (n = 4) were white (further information on the IMPAACT study can be found in Appendix A and Appendix B of the full dossier assessment).

### **Approach of the company to transfer study results of adult patients to the paediatric patient population**

Besides the single-arm IMPAACT study, the company used the SAILING study, which had been conducted in adults, to transfer the results of adult patients to the paediatric target population.

The SAILING study was an RCT already presented by the company for benefit assessment A14-08 [5]. Based on the SAILING study, the G-BA had derived an indication of a minor added benefit of dolutegravir for ART-experienced adults with HIV infection for whom treatment with an integrase inhibitor is the first treatment option. The G-BA had determined that an added benefit is not proven for the group of patients aged 12 to 18 years [3,4].

The SAILING study compared dolutegravir with raltegravir, in each case in addition to individually optimized antiretroviral background therapy. A detailed description of the study design and of the study results can be found in dossier assessment A14-08 [5].

The company justified transferring results of the adult patient population to the paediatric target population with comparable drug levels in children and adults. The company therefore considered transferring results from RCTs in adults to be possible.

The company's approach for transferring results was inadequate. The following aspects in particular were decisive for this:

- The ACT specified by the G-BA in the therapeutic indication of children from  $\geq 6$  to  $< 12$  years of age was not investigated at all. The company conducted no information retrieval for the ACT for further investigations. As a result, a single-arm study with raltegravir in pretreated children was not considered, for example. This study was cited by the company itself in its clinical study report on the IMPAACT study [14,15]. This raltegravir study is of particular interest especially also because raltegravir had been used as comparator intervention in the SAILING study, which the company used for transferring the results for adults to children.
- The data of the single-arm study IMPAACT presented in the therapeutic indication for children were incomplete. There was no presentation of all relevant outcomes at week 48, which is also required for a comparison with the 48-week results of the SAILING study in adults. It would have been possible for the company to present all outcomes completely because the company itself cited a poster publication from 2016 containing data at week 48 [16].

- The dossier contained no comparison of the patient characteristics or of the results of patient-relevant outcomes between the single-arm study IMPAACT in children and the RCT SAILING in adults. Correspondingly, there was no critical investigation of the differences observed between children and adults. Such an investigation of the studies presented by the company would provide a reason against transferability of the study results to children:
  - The patient characteristics of the children in the IMPAACT study partly differed markedly from those of the adults in the SAILING study regarding ethnicity and disease severity (see Appendix B of the full dossier assessment). Only 17% of the child population was white, whereas this number was 50% in the adult population. The proportion of patients who already had AIDS was almost twice as high in the adult population as in the child population (49% versus 26%). At the start of the study, only 22% of the children, but 72% of the adults had a cluster of differentiation 4 (CD4) cell count below 350/ $\mu$ L. The opposite situation occurred regarding viral load: The proportion of patients with a baseline viral load of  $\geq 50\,000$  HIV-1 ribonucleic acid (RNA) copies/mL was about twice as high in children as in adults (61% versus 30%).
  - The data presented did not support transferability of the treatment effects from the first assessment A14-08 in adults. In pretreated adults, the added benefit of dolutegravir was based on lesser harm in the outcomes “severe AEs grade 3–4 (DAIDS)” and “nervous system disorders” [5]. The comparison of severe AEs grade 3–4 (DAIDS) at week 48 between the studies IMPAACT (data from poster publication) in children and SAILING in adults showed a notably larger proportion of patients with event in the IMPAACT study (17.4%) than in the dolutegravir arm of the SAILING study (9.8%). For nervous system disorders, the SAILING study showed an effect modification by age. Lesser harm from dolutegravir was only shown in older patients ( $\geq 50$  years), but not in younger patients ( $< 50$  years).
  - In addition, the company did not present any results on AIDS-defining events, although it was known from the dossier assessments A14-08 and A14-34 that this outcome was considered to be patient-relevant [5,17].
- The company did not show that integrase inhibitors were the first treatment option in the sense of individual antiretroviral therapy for the children in the IMPAACT study. The G-BA had determined an added benefit of dolutegravir on the basis of the SAILING study only for this subpopulation of pretreated patients. This was because, in the SAILING study, treatment with an integrase inhibitor (dolutegravir or raltegravir) was considered to be individually optimized treatment because the patients included were resistant to at least 2 drug classes [5]. For the IMPAACT study, there was no information on resistances at the start of the study.

### 2.4.2 Results on added benefit

In its dossier, the company did not present any suitable data for the assessment of the added benefit of dolutegravir versus the ACT in pretreated children from  $\geq 6$  to  $< 12$  years of age. This resulted in no hint of an added benefit of dolutegravir in comparison with the ACT; an added benefit is therefore not proven.

### 2.4.3 Probability and extent of added benefit

Since the company did not present any suitable data for the assessment of the added benefit of dolutegravir in comparison with the ACT in pretreated HIV-infected children from  $\geq 6$  to  $< 12$  years of age, an added benefit of dolutegravir is not proven for these patients.

### 2.4.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

## 2.5 Probability and extent of added benefit – summary

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

Research question	Subindication	ACT <sup>a</sup>	Probability and extent of added benefit
1	Treatment-naive children from $\geq 6$ to $< 12$ years of age	ART consisting of 2 NRTIs (abacavir or lamivudine or emtricitabine or zidovudine) and 1 NNRTI (efavirenz or nevirapine) or 1 protease inhibitor (lopinavir or atazanavir or darunavir, each in combination with ritonavir)	Added benefit not proven
2	ART-experienced children from $\geq 6$ to $< 12$ years of age	Individual ART based on prior treatment(s) and under consideration of 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.  
 ACT: appropriate comparator therapy; ART: antiretroviral therapy; G-BA: Federal Joint Committee;  
 NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor

An added benefit of dolutegravir is not proven because the company did not present any suitable data.

This deviates from the approach of the company, which derived a hint of a non-quantifiable added benefit in the present therapeutic indication of pretreated and treatment-naive children from  $\geq 6$  to  $< 12$  years of age. The company's assessment was based on its attempt to transfer results for adult patients to the paediatric target population.

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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