IQWiG Reports – Commission No. A17-37

Dolutegravir (HIV infection) –

Addendum to Commission A17-11[1]

Addendum

Commission: A17-37
Version: 1.0
Status: 30 August 2017

[1] Translation of addendum A17-37 *Dolutegravir (HIV-Infektion) – Addendum zum Auftrag A17-11* (Version 1.0; Status: 30 August 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Dolutegravir (HIV infection) – Addendum to Commission A17-11

Commissioning agency:
Federal Joint Committee

Commission awarded on:
10 August 2017

Internal Commission No.:
A17-37

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum[2]:

- Ulrike Seay
- Christoph Schürmann
- Beate Wieseler

Keywords: dolutegravir, HIV infections, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables

Page

List of figures

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AIDS	Acquired Immunodeficiency Syndrome
ART	antiretroviral therapy
AEs	adverse events
DAIDS	Division of AIDS
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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)
SOC	System Organ Class

1 Background

On 10 August 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-11 (Dolutegravir – Benefit assessment according to §35a Social Code Book V [1]).

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") tried to transfer the results of the studies conducted in adults to the target population of children to assess the added benefit of dolutegravir in comparison with the appropriate comparator therapy (ACT) in children from ≥ 6 to < 12 years of age infected with HIV. The concrete implementation was inadequate, however. Hence no added benefit of dolutegravir in comparison with the ACT in children could be derived.

With its written comment on the dossier assessment [3], the company submitted further data. The G-BA commissioned IQWiG with the assessment of these data.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Research question 1: treatment-naive children from ≥ 6 to < 12 years of age

In its dossier, the company presented no data for children, but tried to transfer the results of the two dolutegravir studies SPRING-1 and SINGLE conducted in treatment-naive adults to the target population of the children. The studies SPRING-1 and SINGLE were already known from a previous benefit assessment of dolutegravir in adults [4]. In these randomized controlled trials (RCTs), the patients in the comparator arms were treated with the ACT specified for treatment-naive adults. This concurs only partially with the ACT for children. Only in the SPRING-1 study, a small proportion of the adult patients were treated with the backbone therapy for children (abacavir + lamivudine) (N = 17 in the dolutegravir arm and N = 16 in the efavirenz arm of the study). In the framework of the commenting procedure, the company presented analyses of these patients [3]. However, the data presented were incomplete. On the one hand, the patient characteristics were not presented. On the other hand, the company did not submit analyses for all patient-relevant outcomes. Analyses for the outcomes "severe AEs grade 3–4 (Division of AIDS, [DAIDS])", "psychiatric disorders" (System Organ Class [SOC]) as well as "musculoskeletal and connective tissue disorders" (SOC) are missing.

The data submitted by the company are shown in Appendix A as presented by the company.

Since data for treatment-naive children in the therapeutic indication are still missing, it could not be investigated in how far effects in adults can be transferred to children.

2.2 Research question 2: pretreated children from ≥ 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 ≥ 6 to < 12 years of age in its dossier. The SAILING study was already known from a previous benefit assessment of dolutegravir in adults [4]. 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). The company's attempt to transfer the results of the SAILING study to children was insufficient. Detailed reasons can be found in dossier assessment A17-11 [1].

With its comment, the company presented analyses of the single-arm raltegravir study IMPAACT P1066 for children. The children in the cohorts II A (N = 4) and II B (N = 13) concurred with the therapeutic indication investigated in the present research question. The company already presented the results of cohort II A of the dolutegravir study IMPAACT P0193, which also included the population of children relevant for the present research question, in its dossier. In its comment, the company provided a descriptive presentation of the patient characteristics and the results of the two cohorts II A and II B of the study IMPAACT P1066 and of cohort II A of the study IMPAACT P0193.

The approach of the company was inadequate. The company did not show that the added benefit of dolutegravir in adults can be transferred to children from 6 to 12 years of age. The reasons are as follows:

- There was no comparison of the patient characteristics of the single-arm studies IMPAACT P0193 (dolutegravir) and IMPAACT P1066 (raltegravir) in children with those of the RCT SAILING in adults, which would be required to substantiate a transferability. Correspondingly, there was no critical investigation of the differences observed between children and adults. Dossier assessment A17-11 already showed that such an investigation of the studies presented by the company for dolutegravir provided reasons against a transferability of the study results to children [1].
- Furthermore, there was no comparison of the results of the single-arm studies IMPAACT P0193 (dolutegravir) and IMPAACT P1066 (raltegravir) in children with the results of the corresponding arms of the RCT SAILING in adults. The added benefit of dolutegravir shown in dossier assessment A14-08 is based on an advantage in favour of dolutegravir for the outcome "severe AEs grade 3–4 (DAIDS)". At a purely numerical consideration of the data, the events for the outcome "severe AEs grade 3–4 (DAIDS)" presented in Table 1 contradict a transferability of the results for adults to children.
- The company did not show that integrase inhibitors were the first treatment option in the sense of individual antiretroviral therapy (ART) for the children in the studies IMPAACT P0193 and IMPAACT P1066 (see also dossier assessment A17-11) and that raltegravir would thus be a suitable ACT.

The analyses subsequently submitted by the company are shown in Appendix B, Figure 2 and Figure 3, as presented by the company.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit from dossier assessment A17-11: The added benefit of dolutegravir in comparison with the ACT is not proven.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dolutegravir (HIV-Infektion): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-11 [online]. 28.06.2017 [Accessed: 05.07.2017]. (IQWiG-Berichte; Volume 518). URL: https://www.iqwig.de/download/A17-11_Dolutegravir_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. ViiV Healthcare. Dolutegravir (Tivicay): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 16.03.2017 [Accessed: 19.07.2017]. URL: https://www.g-ba.de/informationen/nutzenbewertung/281/.

3. ViiV Healthcare. Stellungnahme zum IQWiG-Bericht Nr. 514: Dolutegravir (HIV-Infektion); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-11. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/281/ in the document "Zusammenfassende Dokumentation"].

4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dolutegravir: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-08 [online]. 12.05.2014 [Accessed: 18.05.2017]. (IQWiG-Berichte; Volume 221). URL: https://www.iqwig.de/download/A14-08_Dolutegravir_Nutzenbewertung-35a-SGB-V.pdf.

5. Wiznia A, Alvero C, Fenton T, George K, Townley E, Harzra R et al. IMPAACT 1093: dolutegravir in 6- to 12-year-old HIV-infected children; 48-week results [online]. In: Conference on Retroviruses and Opportunistic Infections; 22.-25.02.2016; Boston, USA. 25.02.2016 [Accessed: 16.01.2017]. URL: http://www.croiconference.org/sessions/impaact-1093-dolutegravir-6-12-year-old-hiv-infected-children-48-week-results.

Appendix A – Research question 1: treatment-naive children

Table: Results of RCT ING112276 (Spring-1) study at outcome level – treatment-naive patients with the background therapy abacavir + lamivudine

Outcome	**Parameter**	**Results Dolutegravir 50 mg qd + abacavir/lamivudine Safety population (N = 17)**	**Results Efavirenz 600 mg + abacavir/lamivudine Safety population (N = 16)**
Morbidity			
Virologic response (<50 HIV RNA copies/mL) at week 96	Proportion of patients with virologic response (%)	88%	73%
Change of the number of the CD4 cells compared with baseline (absolute) at week 96 (cells/mm^3)	Number of patients mean (SD) median (min-max)	15 303.0 (207.71) 254.0 (-4; 782)	11 437.2 (156.44) 445.0 (231; 815)
Adverse events			
Total adverse events	Number* n (%)	16 (94)	16 (100)
	Relative risk (95% CI)**	0.94 [0.84; 1.06]	
Serious adverse events (without deaths)	Number* n (%)	2 (12)	4 (25)
	Relative risk (95% CI)**	0.47 [0.10; 2.23]	
Study discontinuation due to adverse events	Number* n (%)	1 (6)	4 (25)
	Relative risk (95% CI)**	0.24 [0.03; 1.89]	
Aids-defined events	Number* n (%)	1 (6)	0
Adverse events of particular interest			
Skin rash	Number* n (%)	0	3 (19)
Nervous system disorders	Number* n (%)	2 (12)	8 (50)
	Relative risk (95% CI)**	0.24 [0.06; 0.95]	

* Patients with at least one adverse event
** Institute's calculation

Figure 1: Results of the SPRING-1 study - treatment-naive patients with the background therapy abacavir + lamivudine – Table from subsequently submitted analyses of the company

Appendix B – Research question 2: pretreated children

Table 1: Severe AEs grade 3–4 (DAIDS) in the studies on dolutegravir and raltegravir in children (≥ 6 to < 12 years) and adults

Study Observation period	Dolutegravir		Raltegravir	
	N	Patients with event n (%)	N	Patients with event n (%)
SAILING (adults)[a] 48 weeks	357	35 (9.8)	362	53 (14.6)
IMPAACT P1093 (children)[b] Cohort II A at least 24 weeks[c]	23	2 (8.7)		
IMPAACT P1093 (children)[d] Cohort II A 48 weeks	23	4 (17.4)		
IMPAACT P1066 (children)[b] Cohort II A and II B at least 48 weeks	17			2 (11.8)

a: Information from dossier assessment A14-08 [4].
b: Data presented by the company with the comments [3].
c: Treatment time with the study medication in 22 of the 23 patients in cohort IIA longer than 24 weeks, and in 16 patients longer than 48 weeks (information from the company's comment).
d: Data from a poster publication [5] in the company's dossier.
N: number of analysed patients; n: number of patients with (at least 1) event; AEs: adverse events

Table 1: Characteristics of the study populations – further investigations with the drug under assessment – therapeutic indication

Study **Group** **Population**	**N**	**Age** **(years)** **mean (SD)**	**Sex** **(f / m)** **N (%)**	**Weight** **(kg)** **mean (SD)**	**Race** **N (%)**		**Ethnicity** **N (%)**	
IMPAACT (P1093) Cohort IIA AT population	23	9.0 (2.0)	7 (30.4) 16 (69.6)	30.1 (10.4)	Asian Hawaiian Black White More than one race unknown	3 (13.0) 1 (4.3) 12 (52.2) 4 (17.4) 1 (4.3) 2 (8.7)	Hispanic or Latino No Hispanic or Latino unknown	6 (26.1) 13 (56.5) 4 (17.4)
IMPAACT (P1066) Cohort IIA Final dose population	4	10.0 (1.4)	1 (25.0) 3 (75.0)	Not reported	Black or African American White	3 (75) 1 (25)	Hispanic or Latino	1 (25)
IMPAACT (P1066) Cohort IIB Final dose population	13	8.8 (1.)	6 (46.2) 7 (53.8)	Not reported	Black or African American White	7 (53.8) 6 (46.2)	Hispanic or Latino	7 (53.8)
Source: ([20]GSK. 2015 SAS Table 7, SAS Table 8;[28]Nachman; et al., 2013)								

Figure 2: Characteristics of the study populations – further investigations with the drug under assessment – table from subsequently submitted analyses of the company

Study Group Population	N	Plasma HIV RNA		CD4 cell count		CD8 cell count	
		Copies/mL		log10 copies/mL Mean (SD)	Cells/mm³ Mean (SD)	% Mean (SD)	Cells/mm³ Mean (SD)	% Mean (SD)
IMPAACT (P1093) Cohort IIA AT population	23	400 - < 5000 5000 - < 10 000 10 000 - < 25 000 25 000 - < 50 000 ≥ 50 000	4 (17.4) 1 (4.3) 0 (0) 4 (17.4) 14 (60.9)	4.9 (1.0)	621.3 (376.2)	22.0 (11.6)	1345.2 (614.5)	50.8 (12.8)
IMPAACT (P1066) Cohort IIA Final dose population	4	1000 - ≤ 4000 > 4000 - ≤ 50 000 > 50 000	1 (25.0) 2 (50.0) 1 (25.0)	4.4 (0.6)	850.5 (509.5)	25.2 (8.7)	Not reported	Not reported
IMPAACT (P1066) Cohort IIB Final dose population	13	1000 - ≤ 4000 > 4000 - ≤ 50 000 > 50 000	1 (7.7) 9 (69.2) 3 (23.0)	4.2 (0.5)	577.9 (269.8)	29.1 (10.4)	Not reported	Not reported
Source: ([20]GSK. 2015 SAS Table 8)								

Figure 2: Characteristics of the study populations – further investigations with the drug under assessment – table from subsequently submitted analyses of the company (continued)

Table 2: Results of the studies IMPAACT (P193) and IMPAACT (P1066) in the therapeutic indication at outcome level

Outcome	**Parameter**	**Results IMPAACT (P1093) Cohort IIA AT population (N = 23)**	**Results IMPAACT (P1066) Cohort IIA Final dose population (N = 4)**	**Results IMPAACT (P1066) Cohort IIB Final dose population (N = 13)**
Mortality				
Deaths	Number n (%)	0	0	0
Morbidity				
Virologic response (<50 HIV RNA copies/mL) at week 24	Number of patients with virologic response Number of patients (%) (95% confidence interval)	14 60.9% (38.5; 80.3)	2 50.0% (6.8; 93.2)	7 53.8% (25.1; 80.8)
Change of the number of CD4 cells compared with baseline (absolute) at week 24	Number of patients Median (min-max) (cells/mm^3) Mean (95% confidence interval)	21 209.00 (-462.00- 725.00) Not reported	4 Not reported -35.8 (-348.8; 277.3)	13 Not reported 143.4 (-12.9; 299.6)
Change of the number of CD4 cells compared with baseline (relative) at week 24	Number of patients Median (min-max) (%) Mean (95% confidence interval)	21 8.0 (-4.50-21.00) Not reported	4 Not reported 2.2 (-7.2; 11.5)	13 Not reported 0.8 (-3.6; 5.2)
Change of the number of CD4 cells compared with baseline (absolute) at week 48	Number of patients Median (min-max) (cells/mm^3) Mean (95% confidence interval)	15 373.00 (-441.00-980.00) Not reported	4 Not reported 189.5 (-154.2; 533.2)	11 Not reported 76.8 (-85.3; 238.9)
Change of the number of CD4 cells compared with baseline (relative) at week 48	Number of patients Median (min-max) (%) Mean (95% confidence interval)	15 9.00 (-0.50-26.00) Not reported	4 Not reported 6.0 (-2.6; 14.6)	11 Not reported 1.6 (-2.7; 5.9)

Figure 3: Results of the studies IMPAACT (P193) and IMPAACT (P1066) in the therapeutic indication at outcome level – table from subsequently submitted analyses of the company

Outcome	**Parameter**	**Results IMPAACT (P1093) Cohort IIA AT population (N = 23)**	**Results IMPAACT (P1066) Cohort IIA Final dose population (N = 4)**	**Results IMPAACT (P1066) Cohort IIB Final dose population (N = 13)**
Resistances to integrase inhibitors.	Patients with resistances n (%) Mutation	1 (4.3) S230N*	Not reported	Not reported
Adverse events* **				
Total adverse events	Number** n (%)	22 (95.7)	4 (100.0)	13 (100.0)
Adverse events grade 3-4	Number** n (%)	2 (8.7)	0 (0.0)	2 (15.4)
Serious adverse events	Number** n (%)	3 (13.0)	0 (0.0)	2 (15.4)
Study discontinuations due to adverse events	Number** n (%)	0	0	0
Adverse event of particular interest				
Hypersensitivity and skin rash	Number** n (%)	1 (4.3)	Not reported	Not reported
Hepatobiliary disorders	Number** n (%)	1 (4.3)	Not reported	Not reported
Psychiatric disorders (including suicidality)	Number** n (%)	3 (13.0)	Not reported	Not reported

Figure 3: Results of the studies IMPAACT (P193) and IMPAACT (P1066) in the therapeutic indication at outcome level – table from subsequently submitted analyses of the company (continued)

Outcome	Parameter	Results IMPAACT (P1093) Cohort IIA AT population (N = 23)	Results IMPAACT (P1066) Cohort IIA Final dose population (N = 4)	Results IMPAACT (P1066) Cohort IIB Final dose population (N = 13)
Gastrointestinal disorders	Number** n (%)	10 (43.5)	Not reported	Not reported
Musculoskeletal, connective tissue disorders	Number** n (%)	3 (13.0)	Not reported	Not reported
Renal and urinary disorders	Number** n (%)	2 (8.7)	Not reported	Not reported

* Mutation S230N is rated as non resistance-conferring
** Patients with at least 1 adverse event
*** IMPAACT (P1093): Proportion of patients for whom at least 1 adverse event was reported within the framework of the study until the data cut-off on 14 February 2015. At this time point, the treatment time with the study medication was longer than 24 weeks in 22 of the 23 patients in cohort IIA, and longer than 48 weeks in 16 patients
IMPAACT (P1066): Proportion of patients for whom at least 1 adverse event was reported within the framework of the study until the data cut-off on 7 February 2013.

Sources: ([20]GSK. 2015[28] SAS Nachman, et al. 2013. [30]clinicaltrials.gov. 2017)

Figure 3: Results of the studies IMPAACT (P193) and IMPAACT (P1066) in the therapeutic indication at outcome level – table from subsequently submitted analyses of the company (continued)