IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Rilpivirine (new therapeutic indication) – Addendum to Commission A15-55[1]

Addendum

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

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Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV-1	human immunodeficiency virus type 1
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NRTI	nucleoside reverse transcriptase inhibitors
RNA	ribonucleic acid
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 9 May 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-55 (Rilpivirine [new therapeutic indication] – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The dossier assessment A15-55 was conducted due to a change in the therapeutic indication of rilpivirine [1]. This change referred to antiretroviral treatment-naive children and adolescents between ≥ 12 and < 18 years of age with human immunodeficiency virus type 1 (HIV-1) infection and a viral load of ≤ 100 000 HIV-1 ribonucleic acid (RNA) copies/mL [2]. The pharmaceutical company (hereinafter referred to as "the company") had submitted a one-arm study on rilpivirine (study TM 278-C213, hereinafter referred to as "study C213") in its dossier. The company did not aim to conduct an indirect comparison of rilpivirine with the appropriate comparator therapy (ACT) [3].

To be able to make a decision on the added benefit of rilpivirine, the G-BA commissioned IQWiG with the presentation and, if possible, assessment of the one-arm study C213 presented by the company in the dossier. The data were to be presented and assessed under the research question whether the study presented could be used for the assessment of the added benefit of rilpivirine in adolescents aged 12 years and older. If applicable, the information submitted by the company in the commenting procedure was to be used as additional information.

With its written comments [4], the company submitted information on the use of the interventions in the C213 study. Furthermore, it submitted analyses for an unadjusted indirect comparison of rilpivirine with efavirenz.

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

2 Assessment

2.1 Study TM 278-C213

In the dossier, the company presented the one-arm study TM 278-C213 (hereinafter referred to as "study C213") for the benefit assessment of rilpivirine in the new therapeutic indication. This study was described in the dossier assessment on Commission A15-55, including a table on study characteristics [1]. With this one-arm study, the company presented no data from which an added benefit of rilpivirine in comparison with the ACT could be derived. The company did not aim to conduct an indirect comparison of rilpivirine with the ACT (see the detailed description in the dossier assessment on Commission A15-55).

The relevant subpopulation of the C213 study for the present research question comprised 28 of a total of 36 children and adolescents. This population is defined by a viral load of ≤ 100 000 HIV-1 RNA copies/mL (see dossier assessment on Commission A15-55).

Due to missing information for the dossier assessment on Commission A15-55, it remained unclear whether the nucleoside reverse transcriptase inhibitors (NRTIs) in the C213 study were administered in compliance with the approval status valid in Germany.

In its comment, the company presented information for 14 children and adolescents in the C213 study on the NRTIs that were administered together with efavirenz ("backbone" therapy). It could be inferred from this information that one patient who had received lamivudine had received a dose of 150 mg instead of the approved dose of 300 mg [5]. 11 patients had received tenofovir at a dose of 300 mg. This information presumably referred to tenofovir disoproxil fumarate, which corresponds to 245 mg tenofovir disoproxil. This dose is in compliance with the approval [6]. Even though treatment for 14 patients was largely within the German approval status, this remained unclear for the other patients because information was missing. In addition, the company did not describe whether the 14 patients for whom it presented data were part of the relevant subpopulation.

Demographic information on the relevant subpopulation was only available for sex. 11 (39%) of the patients were male, and 17 (61%) were female. The average age in the total population was 14.6 years (standard deviation 1.7). 56% of the patients were female. Cluster of differentiation 4 (CD4) cell count was > 200/µL in about 89% of the 36 patients.

Table 1 shows the results of the one-arm study C213 for the relevant subpopulation.

Table 1: Results – further investigations, one-arm study on rilpivirine (patients with ≤ 100 000 HIV-1 RNA copies/mL at enrolment)

Study	**Rilpivirine**	
Outcome category **Outcome**	**N**	**Patients with event n (%)[a]**
Study C213 (time point: 48 weeks)		
Mortality		
Death	28	0 (0)
Morbidity		
Virologic response (< 50 HIV-1 RNA copies/mL)[b]	28	22 (78.6)
Supplementary information: surrogate outcome change in CD4 cell count/µL	28	mean (SD) 214.5 (205.6)
Side effects		
AEs (supplementary information)	28	27 (96.4)
SAEs	28	5 (17.9)
discontinuation due to AEs	28	0 (0)
Further AEs of (SOC)[c]		
Gastrointestinal disorders	28	14 (50)
Infections and infestations	28	23 (82.1)
Psychiatric disorders	28	7 (25.0)
Nervous system disorders	28	10 (35.7)
Respiratory, thoracic and mediastinal disorders	28	9 (32.1)

a: Unless otherwise stated.
b: According to FDA-TLOVR algorithm
c: The choice of AEs of particular interest based on SOCs presented by the company in Module 4 of the dossier was not comprehensible. In the present table, the SOCs in which an event was observed in at least 20% of the patients are presented. The SOC "investigations" is not presented because it included no patient-relevant events in the C213 study.

AE: adverse event; CD4: cluster of differentiation 4; FDA: Food and Drug Administration; HIV: human immunodeficiency virus; n: number of patients with (at least one) event; N: number of analysed patients; RNA: ribonucleic acid; SAE: serious adverse event; SD: standard deviation; SOC: System Organ Class; TLOVR: time to loss of virologic response; vs.: versus

About 79% of the children and adolescents in the relevant subpopulation in the C213 study showed virologic response; about 18% had a serious adverse event (SAE). The most common adverse events (AEs) by System Organ Class (SOC) were infections and infestations (82.1% of the patients) and gastrointestinal events (50% of the patients).

Since comparator data were missing, no hint of an added benefit resulted from the one-arm study C213; hence there is no proof of an added benefit.

2.2 Unadjusted indirect comparison of rilpivirine and efavirenz

The company submitted an unadjusted indirect comparison of rilpivirine with efavirenz in its comment. For this purpose, it presented 4 one-arm studies on efavirenz (Starr 1999 [7], Starr 2002 [8], McKinney 2007 [9], Scherpbier 2007 [10]). The company considered the outcome "virologic response" for this comparison. It provided no information on information retrieval. The company considered the comparison to be interpretable "to a very limited extent" because of differences in patient characteristics and the methodological limitations of an unadjusted indirect comparison.

Due to the missing description of the information retrieval, it could not be assessed whether the study pool on studies with efavirenz presented by the company was complete.

Table 2 shows the interventions used in the studies presented on efavirenz, the number and age of the patients included, how many of them had not been pretreated with antiretroviral therapy, and information on the number of patients with ≤ 100 000 HIV-1 RNA copies/mL at enrolment.

Table 2: Characteristics of the studies subsequently submitted by the company and the patients included in them – further investigations, one-arm studies on efavirenz

Study	Intervention	Number of patients N	Age Mean (SD) Median (min; max)	Number of treatment-naive patients n (%)	Number of patients with ≤ 100 000 HIV-1 RNA copies/mL at enrolment n (%)
Starr 1999	▪ Efavirenz once daily in the morning, initial dose based on body weight[a] ▪ Nelfinavir 3 times daily, initial dose 20–30 mg/kg Patients could continue treatment with the NRTIs they had been taking before the study, or change them at the physician's discretion.	57	8.5 (3.3) 8.0 (3.8; 16.8)	2 (3.5[b])[c]	ND
Starr 2002	▪ Efavirenz once daily in the morning, initial dose 720 mg based on body weight[d] ▪ Nelfinavir 3 times daily, initial dose: patients ≤ 30 kg: 20–30 mg/kg; patients ≥ 30 kg: 750 mg	19	ND 5.3 (3.1; 9.6)	14 (73.7[b])[c]	ND
McKinney 2007	▪ Efavirenz once daily, dose according to dosing regimen based on body weight (capsule: min dose 200 mg; max dose 600 mg; oral solution: min 360 mg, max 720 mg) ▪ Emtricitabine once daily 6 mg/kg (max dose 200 mg) ▪ Didanosine once daily 240 mg/m^2 (max dose 400 mg)	37	ND 10.5 (3.2; 21.1)[d]	36 (97.3)	ND
Scherpbier 2007	▪ Efavirenz once daily, dose according to dosing regimen either based on age as suspension or based on body weight as capsule (capsule: min dose 200 mg, max dose 600 mg) ▪ Abacavir 16 mg/kg (max dose 600 mg daily) ▪ Didanosine once daily, 200–400 mg/m^2 ▪ Lamivudine 4 mg/kg (< 6 weeks) or 8 mg/kg (≥ 6 weeks); max dose 300 mg daily	36	ND 6.6 (IQR: 3.3; 10.7)[f] Treatment-naive: 3.3 (IQR: 1.7; 9.9)[f]	14 (38.9)[e]	ND

(continued)

Table 2: Characteristics of the studies subsequently submitted by the company and the patients included in them – further investigations, one-arm studies on efavirenz (continued)

a: Initial dose (mg/day) = (body weight/70)$^{0.7}$ * 600 mg; the dose was rounded to 25 mg.
b: Institute's calculation.
c: Pretreatment with NNRTI or PI was an exclusion criterion of the study.
d: Initial dose (mg/day) = (body weight/70)$^{0.7}$ * 720 mg.
d: Baseline data are also presented for the age group (median [min; max]): 17.5 (14.5; 21.1), no results are available for them.
e: No patients had received previous NNRTI.
f: IQR: first quartile; third quartile.
HIV: human immunodeficiency virus; IQR: interquartile range; max: maximum; min: minimum; N: number of patients included; ND: no data; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; RNA: ribonucleic acid; SD: standard deviation; vs.: versus

The studies on efavirenz presented by the company represented neither the ACT nor the therapeutic indication of rilpivirine:

- None of the studies used the ACT consisting of the combination of efavirenz with abacavir plus lamivudine. Patients received efavirenz in all 4 studies, but abacavir and lamivudine were only administered in the Scherpbier 2007 study; this study also used didanosine, however. In the other 3 studies, efavirenz was combined either with nelfinavir or with emtricitabine and didanosine.
- The patients in all 4 studies were – mostly – younger than 12 years.
- McKinney 2007 was the only study in which almost all patients included had not received antiretroviral pretreatment. In the other studies, the proportion of antiretroviral treatment-naive patients was between about 4% and 74%.
- Information on the number of patients with ≤ 100 000 HIV-1 RNA copies at enrolment was not available for any of the studies.

Overall, an adjusted indirect comparison for the present research question was not possible with the studies on efavirenz presented by the company. This deviates from the assessment of the company, which also saw differences in age and pretreatment, but only considered the indirect comparison with the studies presented to be interpretable "to a very limited extent".

2.3 Summary

The data presented by the company were unsuitable for the benefit assessment of rilpivirine versus the ACT. This applied both to the data already presented with the dossier, and for the data subsequently submitted in the comment.

In summary, the data additionally presented by the company did not change the assessment of dossier assessment A15-55: The added benefit in comparison with the ACT is not proven for rilpivirine in combination with other antiretroviral drugs for the treatment of HIV-1 infection

in antiretroviral treatment-naive children and adolescents between ≥ 12 and < 18 years of age with a viral load of ≤ 100 000 HIV-1 RNA copies/mL.

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