

IQWiG Reports – Commission No. A15-55

**Rilpivirine (new therapeutic  
indication) –  
Benefit assessment according to  
§35a Social Code Book V<sup>1</sup>**

**Extract**

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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](mailto:berichte@iqwig.de)

Internet: [www.iqwig.de](http://www.iqwig.de)

**Medical and scientific advice:**

- Ingo Niemetz, practice, Kassel, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

**IQWiG employees involved in the dossier assessment<sup>2</sup>:**

- Katharina Biester
- Gertrud Egger
- Miriam Luhn
- Sarah Mostardt
- Christoph Schürmann
- Dorothea Gechter
- Volker Vervölgyi

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<sup>2</sup> Due to legal data protection regulations, employees have the right not to be named.

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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
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 inhibitor
RCT	randomized controlled trial
RNA	ribonucleic acid
SGB	Sozialgesetzbuch (Social Code Book)

## 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 rilpivirine. 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 21 December 2015.

#### Research question

The aim of the present report was to assess the added benefit of rilpivirine in comparison with efavirenz in combination with abacavir and lamivudine as appropriate comparator therapy (ACT) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve children and adolescents between  $\geq 12$  and  $< 18$  years of age with a viral load  $\leq 100\,000$  HIV-1 ribonucleic acid (RNA) copies/mL (see Table 2).

Table 2: Rilpivirine – research question of the benefit assessment

Research question	Therapeutic indication	Intervention	ACT <sup>a</sup>
1	In combination with other antiretroviral drugs for the treatment of HIV-1 infection in antiretroviral treatment-naïve children and adolescents between $\geq 12$ and $< 18$ years of age with a viral load $\leq 100\,000$ HIV-1 RNA copies/mL <sup>b</sup>	Rilpivirine	Efavirenz in combination with abacavir plus lamivudine
a: Presentation of the appropriate comparator therapy specified by the G-BA. The company followed this ACT. b: As with other antiretroviral drugs, genotypic resistance testing should guide the use of rilpivirine. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; RNA: ribonucleic acid			

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Studies with a minimum duration of 48 weeks were relevant for the derivation of the added benefit.

#### Results

The company presented no data from which an added benefit of rilpivirine in comparison with the ACT could be derived. Due to a lack of randomized controlled trials (RCTs), the company included a one-arm study on rilpivirine in its assessment (study TM 278-C213, hereinafter referred to as “study C213”). The company did not aim to conduct an indirect comparison of rilpivirine with the ACT.

Conclusions on the added benefit based on one-arm study designs are only possible in the presence of very large effects (so-called dramatic effects) regarding patient-relevant outcomes. To derive such an effect, the C213 study first would have to be generally suitable to provide information on rilpivirine for the research question of the benefit assessment. Moreover, sufficiently certain data on the ACT for the corresponding outcomes are necessary to be able to estimate the size of the effect. Finally, the effect estimated on the basis of the available data has to be so large that it can be excluded that it is solely caused by systematic bias.

The C213 study included by the company was a one-arm study including 36 antiretroviral treatment-naïve children and adolescents between  $\geq 12$  and  $< 18$  years of age with HIV-1 infection. 28 of the 36 patients constituted the subpopulation potentially relevant for the present research question because they had a viral load of  $\leq 100\,000$  HIV-1 RNA copies/mL. 89% of the total population were black/African American patients, and 11% were Asian patients. No information was available on the ethnicity of the potentially relevant subpopulation. All patients received rilpivirine combined with 2 nucleoside reverse transcriptase inhibitors (NRTIs): rilpivirine with emtricitabine and tenofovir (20 of the 28 patients), rilpivirine with lamivudine and tenofovir (6 of the 28 patients), and rilpivirine with lamivudine and zidovudine (2 of the 28 patients). The dosages of the NRTIs remained unclear. It could therefore not be verified whether the NRTIs were used in compliance with the approval status valid in Germany. The primary analysis was conducted after 24 weeks; a second analysis was conducted after 48 weeks.

The company presented no data for the ACT; it also did not search for them and hence did not address effects (group differences between rilpivirine and the ACT). Irrespective of the missing data, the company derived an added benefit of rilpivirine of non-quantifiable extent.

Based on the data on rilpivirine from the one-arm study C213 presented by the company, with missing information on the ACT and the corresponding lack of the investigation of effects, no conclusion on the added benefit was possible.

Besides the reasons mentioned above, the suitability of the data on rilpivirine presented by the company remained unclear, and the completeness of the search results on data on rilpivirine from one-arm studies could not be guaranteed.

### Extent and probability of added benefit, patient groups with therapeutically important added benefit<sup>4</sup>

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

Table 3: Rilpivirine – extent and probability of added benefit

Therapeutic indication	ACT <sup>a</sup>	Extent and probability of added benefit
In combination with other antiretroviral drugs for the treatment of HIV-1 infection in antiretroviral treatment-naïve children and adolescents between $\geq 12$ and $< 18$ years of age with a viral load $\leq 100\,000$ HIV-1 RNA copies/mL <sup>b</sup>	Efavirenz in combination with abacavir plus lamivudine	Added benefit not proven
<p>a: Presentation of the appropriate comparator therapy specified by the G-BA. The company followed this ACT.</p> <p>b: As with other antiretroviral drugs, genotypic resistance testing should guide the use of rilpivirine.</p> <p>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; RNA: ribonucleic acid</p>		

The G-BA decides on the added benefit.

<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].

## 2.2 Research question

The aim of the present report was to assess the added benefit of rilpivirine in comparison with efavirenz in combination with abacavir and lamivudine as ACT for the treatment of HIV-1 infection in antiretroviral treatment-naïve children and adolescents between  $\geq 12$  and  $< 18$  years of age with a viral load  $\leq 100\,000$  HIV-1 RNA copies/mL (see Table 4).

Table 4: Rilpivirine – research question of the benefit assessment

Research question	Therapeutic indication	Intervention	ACT <sup>a</sup>
1	In combination with other antiretroviral drugs for the treatment of HIV-1 infection in antiretroviral treatment-naïve children and adolescents between $\geq 12$ and $< 18$ years of age with a viral load $\leq 100\,000$ HIV-1 RNA copies/mL <sup>b</sup>	Rilpivirine	Efavirenz in combination with abacavir plus lamivudine
<p>a: Presentation of the appropriate comparator therapy specified by the G-BA. The company followed this ACT.</p> <p>b: As with other antiretroviral drugs, genotypic resistance testing should guide the use of rilpivirine.</p> <p>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; RNA: ribonucleic acid</p>			

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Studies with a minimum duration of 48 weeks were relevant for the derivation of the added benefit. This deviates from the company, which defined a minimum study duration of 24 weeks. Ultimately, this deviation had no consequence because the company presented 48-week data.

## 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 rilpivirine (status: November 2015)
- bibliographical literature search on rilpivirine (last search on 12 November 2015)
- search in trial registries for studies on rilpivirine (last search on 12 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on rilpivirine (last search on 6 January 2016)

No studies suitable for deriving an added benefit of rilpivirine in comparison with the ACT were identified from the steps of information retrieval mentioned. This deviates from the company's approach, which also identified no RCT, but included a one-arm study on

rilpivirine for its assessment (study TM 278-C213, in this report referred to as “study C213”) [3]. The company did not aim to conduct an indirect comparison of rilpivirine with the ACT.

The data presented by the company were unsuitable to answer the research question of the benefit assessment.

### **Prerequisite for the derivation of an added benefit based on one-arm studies**

Conclusions on the added benefit based on one-arm study designs are only possible in the presence of very large effects (so-called dramatic effects) regarding patient-relevant outcomes. To derive such an effect, the C213 study first would have to be generally suitable to provide information on rilpivirine for the research question of the benefit assessment. Moreover, sufficiently certain data on the ACT for the corresponding outcomes are necessary to be able to estimate the size of the effect. Finally, the effect estimated on the basis of the available data has to be so large that it can be excluded that it is solely caused by systematic bias.

### **Information on rilpivirine (study C213)**

The characteristics of the C213 study are presented in Appendix A of the full dossier assessment. The one-arm study included 36 antiretroviral treatment-naïve children and adolescents between  $\geq 12$  and  $< 18$  years of age with HIV-1 infection. In the beginning of the study, children and adolescents with a viral load of  $\geq 500$  HIV-1 RNA copies/mL were included; the inclusion criterion was then adapted to  $\leq 100\,000$  HIV-1 RNA copies/mL by way of Amendment. 28 (78%) of the 36 patients included had a baseline viral load of  $\leq 100\,000$  HIV-1 RNA copies/mL. These patients constituted the subpopulation potentially relevant for the present research question. 89% of the total population were black/African American patients, and 11% were Asian patients. No information was available on the ethnicity of the potentially relevant subpopulation. All patients received rilpivirine combined with 2 NRTIs: 24 of the 36 patients received rilpivirine combined with emtricitabine and tenofovir, 8 of the 36 patients rilpivirine combined with lamivudine and tenofovir, and 4 of the 36 patients rilpivirine combined with lamivudine and zidovudine. The respective numbers for the subpopulation potentially relevant were 20, 6 and 2 of the 28 patients. The NRTIs were to be administered at the physician’s choice – depending on the availability and approval in the respective country of the study centre (in study C123: India, South Africa, Thailand, Uganda and USA). The dosages of the NRTIs remained unclear. It could therefore not be verified whether the NRTIs were used in compliance with the approval status valid in Germany. The primary analysis was conducted after 24 weeks; a second analysis was conducted after 48 weeks.

### **Information on the appropriate comparator therapy**

Besides relevant data on rilpivirine, sufficiently certain data on the ACT for the patient-relevant outcomes are required to be able to derive a conclusion on the added benefit. However, the company presented no data for the ACT; it also did not search for them and

hence did not address effects (group differences between rilpivirine and the ACT). The company did not justify its approach.

Irrespective of the missing information on the ACT, the company derived an added benefit of rilpivirine of non-quantifiable extent. It justified the extent by claiming that the added benefit could not be quantified because of lacking RCTs.

## Conclusion

The company's approach was not followed. Based on the data on rilpivirine from the one-arm study C213 presented by the company, with missing information on the ACT and the corresponding lack of the investigation of effects, no conclusion on the added benefit was possible.

Besides the reasons mentioned above, the suitability of the data on rilpivirine presented by the company remained unclear, and the completeness of the search results on data on rilpivirine from one-arm studies could not be guaranteed (see Section 2.7.2.3.1 of the full dossier assessment).

## 2.4 Results on added benefit

No evaluable data were available to assess the added benefit of rilpivirine in comparison with the ACT for the treatment of HIV-1 infection in antiretroviral treatment-naive children and adolescents between  $\geq 12$  and  $< 18$  years of age with a viral load  $\leq 100\,000$  HIV-1 RNA copies/mL. There was no hint of an added benefit of rilpivirine in comparison with the ACT. An added benefit is therefore not proven.

## 2.5 Extent and probability of added benefit

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

Table 5: Rilpivirine – extent and probability of added benefit

Therapeutic indication	ACT <sup>a</sup>	Extent and probability of added benefit
In combination with other antiretroviral drugs for the treatment of HIV-1 infection in antiretroviral treatment-naive children and adolescents between $\geq 12$ and $< 18$ years of age with a viral load $\leq 100\,000$ HIV-1 RNA copies/mL <sup>b</sup>	Efavirenz in combination with abacavir plus lamivudine	Added benefit not proven
<p>a: Presentation of the appropriate comparator therapy specified by the G-BA. The company followed this ACT.</p> <p>b: As with other antiretroviral drugs, genotypic resistance testing should guide the use of rilpivirine.</p> <p>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; RNA: ribonucleic acid</p>		

The assessment of the added benefit deviates from that of the company, which derived a non-quantifiable added benefit without stating probability.

The G-BA decides on the added benefit.

## 2.6 List of included studies

Not applicable as no studies were included in the benefit assessment.

### References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22 April 2015 [accessed: 20 October 2015]. URL:

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2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2015; 58(1): 43-58

3. Janssen Sciences Ireland. A study to evaluate the pharmacokinetics, safety, tolerability, and antiviral efficacy of rilpivirine (TMC278) in human immunodeficiency virus infected adolescents and children aged greater than or equal to 6 years: full text view [online]. In: *ClinicalTrials.gov*. [Accessed: 12 November 2015]. URL:

<https://clinicaltrials.gov/ct2/show/NCT00799864>.

*The full report (German version) is published under <https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-55-rilpivirin-neues-anwendungsgebiet-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.7169.html>.*