IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-49

Emtricitabine/rilpivirine/ tenofovir alafenamide (HIV infection) –

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Emtricitabin/Rilpivirin/Tenofoviralafenamid (HIV-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 October 2016). 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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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.

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

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
FTC	emtricitabine
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)
RCT	randomized controlled trial
RNA	ribonucleic acid
RPV	rilpivirine
SGB	Sozialgesetzbuch (Social Code Book)
TAF	tenofovir alafenamide

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 combination emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF). 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 13 July 2016.

Research question

The aim of the present report was to assess the added benefit of FTC/RPV/TAF in comparison with the appropriate comparator therapy (ACT) in adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1) with a viral load ≤ 100 000 HIV-1 ribonucleic acid (RNA) copies/mL.

The G-BA's specification of the ACT for different patient groups resulted in 4 research questions, which are presented in the following Table 2.

Table 2: Research questions of the benefit assessment of FTC/RPV/TAF

Research question	Therapeutic indication	ACT specified by the G-BA
1	Treatment-naive adults[a]	Efavirenz or rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (tenofovir disoproxil plus emtricitabine or abacavir plus lamivudine)
2	Treatment-naive adolescents[a, b]	Efavirenz in combination with abacavir plus lamivudine
3	Pretreated adults[a]	Individual antiretroviral therapy 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
4	Pretreated adolescents[a, b]	

a: With HIV-1 infection and a viral load ≤ 100 000 HIV-1 RNA copies/mL.
b: 12 years of age and older and with a body weight of at least 35 kg.
ACT: appropriate comparator therapy; FTC: emtricitabine; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; RNA: ribonucleic acid; RPV: rilpivirine; TAF: tenofovir alafenamide

For research questions 1 and 3 (treatment-naive and pretreated adults), the company followed the G-BA's specification of the ACT.

The company did not consider research questions 2 and 4 (treatment-naive and pretreated adolescents 12 years of age and older) in its dossier.

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. This concurs with the company's inclusion criteria.

Results

The company presented no data for the assessment of the added benefit of FTC/RPV/TAF in comparison with the ACT for any of the 4 research questions. This resulted in no hint of an added benefit of FTC/RPV/TAF in comparison with the ACT; an added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

The result of the assessment of the added benefit of FTC/RPV/TAF in comparison with the ACT is summarized in Table 3.

Table 3: FTC/RPV/TAF – extent and probability of added benefit

Therapeutic indication	ACT specified by the G-BA	Extent and probability of added benefit
Treatment-naive adults[a]	Efavirenz or rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (tenofovir disoproxil plus emtricitabine or abacavir plus lamivudine)	Added benefit not proven
Treatment-naive adolescents[a, b]	Efavirenz in combination with abacavir plus lamivudine	Added benefit not proven
Pretreated adults[a]	Individual antiretroviral therapy 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
Pretreated adolescents[a, b]		Added benefit not proven
a: With HIV-1 infection and a viral load ≤ 100 000 HIV-1 RNA copies/mL. b: 12 years of age and older and with a body weight of at least 35 kg. ACT: appropriate comparator therapy; FTC: emtricitabine; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; RNA: ribonucleic acid; RPV: rilpivirine; TAF: tenofovir alafenamide		

The G-BA decides on the added benefit.

[4] 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 FTC/RPV/TAF in comparison with the ACT in adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with HIV-1 with a viral load ≤ 100 000 HIV-1 RNA copies/mL.

The G-BA's specification of the ACT for different patient groups resulted in 4 research questions, which are presented in the following Table 4.

Table 4: Research questions of the benefit assessment of FTC/RPV/TAF

Research question	Therapeutic indication	ACT specified by the G-BA
1	Treatment-naive adults[a]	Efavirenz or rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (tenofovir disoproxil plus emtricitabine or abacavir plus lamivudine)
2	Treatment-naive adolescents[a, b]	Efavirenz in combination with abacavir plus lamivudine
3	Pretreated adults[a]	Individual antiretroviral therapy 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
4	Pretreated adolescents[a, b]	

a: With HIV-1 infection and a viral load ≤ 100 000 HIV-1 RNA copies/mL.
b: 12 years of age and older and with a body weight of at least 35 kg.
ACT: appropriate comparator therapy; FTC: emtricitabine; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; RNA: ribonucleic acid; RPV: rilpivirine; TAF: tenofovir alafenamide

For research questions 1 and 3 (treatment-naive and pretreated adults), the company followed the G-BA's specification of the ACT.

The company did not consider research questions 2 and 4 (treatment-naive and pretreated adolescents 12 years of age and older) in its dossier. The company justified this with low patient numbers, among other things. This approach was not followed (see Sections 2.8.1 and 2.8.2.1 of the full dossier assessment). The present assessment was conducted in comparison with the G-BA's ACT.

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 Research question 1: treatment-naive adults

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 list on FTC/RPV/TAF (status: 13 June 2016)
- bibliographical literature search on FTC/RPV/TAF (last search on 13 June 2016)
- search in trial registries for studies on FTC/RPV/TAF (last search on 13 June 2016)

To check the completeness of the study pool:

- search in trial registries for studies on FTC/RPV/TAF (last search on 19 July 2016)

From the steps of information retrieval mentioned, the company identified no studies on FTC/RPV/TAF that allowed an assessment of the added benefit in comparison with the ACT. The Institute's check also identified no relevant study.

Despite the lack of studies on FTC/RPV/TAF, the company derived a hint of a non-quantifiable added benefit of FTC/RPV/TAF for treatment-naive adults. It based its arguments on a postulated transferability of the clinical evidence on the individual drugs (RPV and FTC/TAF) to the combination of FTC/RPV/TAF, which was not supported by suitable clinical data. The company's arguments were unsuitable for the derivation of the added benefit of FTC/RPV/TAF versus the ACT (see Section 2.8.2.8.2 of the full dossier assessment). Since no studies on FTC/RPV/TAF – neither in the free nor in the fixed combination – were available for the assessment of the added benefit, an added benefit of FTC/RPV/TAF is not proven.

2.3.2 Results on added benefit

The company presented no data for the assessment of the added benefit of FTC/RPV/TAF in comparison with the ACT for treatment-naive adults. This resulted in no hint of an added benefit of FTC/RPV/TAF in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of FTC/RPV/TAF for treatment-naive adults, an added benefit of FTC/RPV/TAF in comparison with the ACT for these patients is not proven.

This deviates from the approach of the company, which derived a hint of a non-quantifiable added benefit for these patients on the basis of a postulated transferability of the evidence of the individual drugs (RPV, FTC/TAF) (see Section 2.8.2.8.2 of the full dossier assessment).

2.3.4 List of included studies

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

2.4 Research question 2: treatment-naive adolescents

2.4.1 Information retrieval and study pool

The company did not investigate research question 2 in the dossier. Hence it conducted no information retrieval for research question 2 and presented no data on this.

The Institute's check of completeness on the basis of the company's study list on FTC/RPV/TAF (status: 13 June 2016) and the search in trial registries for studies on FTC/RPV/TAF (last search on 19 July 2016) identified no studies relevant for research question 2.

2.4.2 Results on added benefit

The company presented no data for the assessment of the added benefit of FTC/RPV/TAF in comparison with the ACT for treatment-naive adolescents. This resulted in no hint of an added benefit of FTC/RPV/TAF in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of FTC/RPV/TAF for treatment-naive adolescents, an added benefit of FTC/RPV/TAF in comparison with the ACT for these patients is not proven.

This concurs with the assessment of the company who claimed no added benefit for these patients.

2.4.4 List of included studies

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

2.5 Research question 3: pretreated adults

2.5.1 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 list on FTC/RPV/TAF (status: 13 June 2016)
- bibliographical literature search on FTC/RPV/TAF (last search on 13 June 2016)
- search in trial registries for studies on FTC/RPV/TAF (last search on 13 June 2016)

To check the completeness of the study pool:

- search in trial registries for studies on FTC/RPV/TAF (last search on 19 July 2016)

No relevant study was identified from the check.

2.5.2 Results on added benefit

The company presented no data for the assessment of the added benefit of FTC/RPV/TAF in comparison with the ACT for pretreated adults. This resulted in no hint of an added benefit of FTC/RPV/TAF in comparison with the ACT; an added benefit is therefore not proven.

2.5.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of FTC/RPV/TAF for pretreated adults, an added benefit of FTC/RPV/TAF in comparison with the ACT for these patients is not proven.

This concurs with the assessment of the company who claimed no added benefit for these patients.

2.5.4 List of included studies

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

2.6 Research question 4: pretreated adolescents

2.6.1 Information retrieval and study pool

The company did not investigate research question 4 in the dossier. Hence it conducted no information retrieval for research question 4 and presented no data on this.

The Institute's check of completeness on the basis of the company's study list on FTC/RPV/TAF (status: 13 June 2016) and the search in trial registries for studies on FTC/RPV/TAF (last search on 19 July 2016) identified no studies relevant for research question 4.

2.6.2 Results on added benefit

The company presented no data for the assessment of the added benefit of FTC/RPV/TAF in comparison with the ACT for pretreated adolescents. This resulted in no hint of an added benefit of FTC/RPV/TAF in comparison with the ACT; an added benefit is therefore not proven.

2.6.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of FTC/RPV/TAF for pretreated adolescents, an added benefit of FTC/RPV/TAF in comparison with the ACT for these patients is not proven.

This concurs with the assessment of the company who claimed no added benefit for these patients.

2.6.4 List of included studies

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

2.7 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of FTC/RPV/TAF in comparison with the ACT is summarized in Table 5.

Table 5: FTC/RPV/TAF – extent and probability of added benefit

Therapeutic indication	ACT specified by the G-BA	Extent and probability of added benefit
Treatment-naive adults[a]	Efavirenz or rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (tenofovir disoproxil plus emtricitabine or abacavir plus lamivudine)	Added benefit not proven
Treatment-naive adolescents[a, b]	Efavirenz in combination with abacavir plus lamivudine	Added benefit not proven
Pretreated adults[a]	Individual antiretroviral therapy 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
Pretreated adolescents[a, b]		Added benefit not proven
a: With HIV-1 infection and a viral load ≤ 100 000 HIV-1 RNA copies/mL. b: 12 years of age and older and with a body weight of at least 35 kg. ACT: appropriate comparator therapy; FTC: emtricitabine; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; RNA: ribonucleic acid; RPV: rilpivirine; TAF: tenofovir alafenamide		

The G-BA decides on the added benefit.

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]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

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

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-49-emtricitabine/rilpivirine/tenofovir-alafenamide-hiv-infection-benefit-assessment-according-to-35a-sgb-v.7548.html.