IQWiG Reports – Commission No. A22-52

Doravirine (HIV infection in adolescents) –

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

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Doravirin (HIV-Infektion bei Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 July 2022). 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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Medical and scientific advice

- No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange about how he experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
3TC	lamivudine
ACT	appropriate comparator therapy
AE	adverse event
ART	antiretroviral therapy
DOR	doravirine
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)
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TDF	tenofovir disoproxil fumarate

I 1 Benefit assessment

I 1.1 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 doravirine (DOR). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 2 May 2022.

Research question

The aim of this report was to assess the added benefit of DOR in combination with other antiretroviral drugs in comparison with the appropriate comparator therapy (ACT) in adolescents from 12 years of age and with a body weight of ≥ 35 kg, infected with human immunodeficiency virus type 1 [HIV-1]). The HI viruses must not have mutations known to be associated with resistances to the substance class of the non-nucleoside reverse transcriptase inhibitors (NNRTI).

The research questions shown in Table 2 were derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of DOR

Research question	Therapeutic indication	ACT[a]
1	Treatment-naive adolescents[b] infected with HIV-1[c]	▪ Tenofovir alafenamide + emtricitabine or ▪ abacavir + lamivudine or ▪ abacavir + emtricitabine each in combination with ▫ dolutegravir or ▫ atazanavir/ritonavir or ▫ darunavir/ritonavir or ▫ elvitegravir/cobicistat
2	Pretreated adolescents[b] infected with HIV-1[c]	Individual ART choosing from the approved drugs; under consideration of prior treatment(s) and 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. Presented is the respective ACT specified by the GBA.
b. ≥ 12 years of age and with a body weight of ≥ 35 kg.
c. The HI viruses must not have mutations known to be associated with resistances to the substance class of NNRTI.

ART: antiretroviral therapy; DOR: doravirine; G-BA: Federal Joint Committee; HI: human immunodeficiency; HIV-1: human immunodeficiency virus type 1; NNRTI: non-nucleoside reverse transcriptase inhibitors

Deviating from the G-BA's specification, the company named the following ACT for research question 1:

- Dolutegravir in combination with 2 NRTIs choosing from emtricitabine/tenofovir alafenamide or abacavir/lamivudine (3TC)
- Rilpivirine in combination with emtricitabine/tenofovir disoproxil fumarate (TDF)

The company followed the G-BA's specification on the ACT for research question 2.

Concurring with the G-BA's specification, the present assessment was conducted for both research questions 1 and 2.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum study duration of 48 weeks is required.

Results

Concurring with the company, the check of the completeness of the study pool produced no randomized controlled trials (RCTs) with HIV-1-infected adolescents from 12 years of age on the comparison of DOR versus the ACT.

In the dossier, under "further studies", the company presented data from the IMPAACT 2014 study, on the basis of which approval was granted for adolescents aged 12 years and older in the present therapeutic indication. The company conducted no information retrieval for further investigations.

IMPAACT 2014 is an ongoing single-arm, study conducted in two cohorts with DOR in HIV-1 infected adolescents aged ≥ 12 to < 18 years with a body weight of ≥ 35 kg. The study included both treatment-naive patients and patients who had already received antiretroviral therapy (ART). In Module 4 A of the dossier, the company provides a descriptive presentation of the results on both cohorts under "further investigations". In doing so, it presents the results for cohort 2 both separately by the treatment status (treatment-naive, pretreated) and for cohort 2 as a whole. Based on the non-comparative data of the IMPAACT 2014 study, the company derived a hint of a non-quantifiable added benefit of DOR for both treatment-naïve and pretreated adolescents with HIV-1 infection aged ≥ 12 to < 18 years.

In its dossier, the company therefore presented no suitable data to assess the added benefit of DOR in combination with other antiretroviral drugs in treatment-naive and pretreated adolescents with HIV-1 infection from 12 years of age with a body weight of ≥ 35 kg versus the ACT defined by the G-BA for each of the 2 research questions. For both research questions, this resulted in no hint of an added benefit of DOR in comparison with the ACT; an added benefit is therefore not proven in either case.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

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

Table 3: DOR – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Treatment-naive adolescents[b] infected with HIV-1[c]	▪ Tenofovir alafenamide + emtricitabine or ▪ abacavir + lamivudine or ▪ abacavir + emtricitabine each in combination with ▫ dolutegravir or ▫ atazanavir/ritonavir or ▫ darunavir/ritonavir or ▫ elvitegravir/cobicistat	Added benefit not proven
2	Pretreated adolescents[b] infected with HIV-1[c]	Individual ART choosing from the approved drugs; under consideration of prior treatment(s) and 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. Presented is the respective ACT specified by the GBA.
b. ≥ 12 years of age and with a body weight of ≥ 35 kg.
c. The HI viruses must not have mutations known to be associated with resistances to the substance class of NNRTI.

ART: antiretroviral therapy; DOR: doravirine; G-BA: Federal Joint Committee; HI: human immunodeficiency; HIV-1: human immunodeficiency virus type 1; NNRTI: non-nucleoside reverse transcriptase inhibitors

The G-BA decides on the added benefit.

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

I 1.2 Research question

The aim of this report was to assess the added benefit of DOR in combination with other antiretroviral drugs in comparison with the ACT in adolescents from 12 years of age and with a body weight of ≥ 35 kg, infected with HIV-1). The HI viruses must not have mutations known to be associated with resistances to the substance class of the NNRTI.

The research questions shown in Table 4 were derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of DOR

Research question	Therapeutic indication	ACT[a]
1	Treatment-naive adolescents[b] infected with HIV-1[c]	▪ Tenofovir alafenamide + emtricitabine or ▪ abacavir + lamivudine or ▪ abacavir + emtricitabine each in combination with ▫ dolutegravir or ▫ atazanavir/ritonavir or ▫ darunavir/ritonavir or ▫ elvitegravir/cobicistat
2	Pretreated adolescents[b] infected with HIV-1[c]	Individual ART choosing from the approved drugs; under consideration of prior treatment(s) and 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. Presented is the respective ACT specified by the GBA.
b. ≥ 12 years of age and with a body weight of ≥ 35 kg.
c. The HI viruses must not have mutations known to be associated with resistances to the substance class of NNRTI.

ART: antiretroviral therapy; DOR: doravirine; G-BA: Federal Joint Committee; HI: human immunodeficiency; HIV-1: human immunodeficiency virus type 1; NNRTI: non-nucleoside reverse transcriptase inhibitors

Deviating from the G-BA's specification, the company named the following ACT for research question 1:

- Dolutegravir in combination with 2 NRTIs choosing from emtricitabine/tenofovir alafenamide or abacavir/3TC, or
- Rilpivirine in combination with emtricitabine/TDF

The company followed the G-BA's specification on the ACT for research question 2.

Concurring with the G-BA's specification, the present assessment was conducted for both research questions 1 and 2.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum study duration of 48 weeks is required. In contrast, the company did not restrict the minimum study duration.

I 1.3 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 DOR (status: 8 March 2022)
- bibliographical literature search on DOR (last search on 9 March 2022)
- search in trial registries/trial results databases for studies on DOR (last search on 1 March 2022)
- search on the G-BA website for DOR (last search on 9 March 2022)

To check the completeness of the study pool:

- search in trial registries for studies on DOR (last search on 13 May 2022); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool produced no RCTs with HIV-1-infected adolescents from 12 years of age on the comparison of DOR versus the ACT. The company conducted no information retrieval for further investigations.

In its dossier, the company presents data of the single-arm study IMPAACT 2014 under "further studies" [3-6] on the basis of which the approval was granted for adolescents aged 12 years and older in the present therapeutic indication. The company conducted no information retrieval for further investigations.

A check of the completeness of the study pool presented by the company for other investigations was foregone because the study submitted by the company under "further investigations" is not suitable for deriving an added benefit of DOR due to the lack of comparison with the ACT. This is explained below.

IMPAACT 2014 study

IMPAACT 2014 is an ongoing single-arm, study conducted in two cohorts with DOR in HIV-1 infected adolescents aged ≥ 12 to < 18 years with a body weight of ≥ 35 kg. The study included both treatment-naive patients and patients who had already received ART.

In cohort 1, of 10 virologically suppressed patients included, 9 adolescents received 100 mg of DOR as a single dose in addition to their ongoing ART (consisting of 1 integrase inhibitor and 2 NRTIs) to investigate pharmacokinetics and safety until day 14. Patients from cohort 1 were allowed to switch to cohort 2.

In cohort 2, patients received DOR orally once daily for 96 weeks as a fixed combination with 3TC and TDF according to the Summary of Product Characteristics for the fixed combination DOR/3TC/TDF [7]. The dosage of DOR in the fixed combination corresponds to the Summary of Product Characteristics for DOR [8]. In addition to 43 pretreated adolescents, cohort 2 included 2 treatment-naive adolescents. In order to be included in the study, treatment-naive patients had to be sensitive to DOR, 3TC and TDF based on a genotypic resistance test. Information on resistances at the start of the study was not available for the pretreated, virologically suppressed adolescents in cohort 2; according to the inclusion criteria, resistance testing was not mandatory for the participation in the study. Primary outcome of cohort 2 are adverse events (AEs) until week 24. Secondary patient-relevant outcomes are AEs until weeks 48 and 96.

Approach of the company

In Module 4 A of the dossier, the company provides a descriptive presentation of the results on both cohorts under "further investigations". In doing so, it presents the results for cohort 2 both separately by the treatment status (treatment-naive, pretreated) and for cohort 2 as a whole. For cohort 1, results on safety (including deaths) are available for week 2; for cohort 2, ^there are data on efficacy until week 48 (last patient visit: 20 January 2021) as well as on safety (including deaths) until the data cut-off of 7 July 2021, i.e. also beyond week 48. The company presented no data on the ACT and made no comparison with the ACT.

Based on the results of the IMPAACT 2014 study, the company derived a hint of a non-quantifiable added benefit of DOR for both treatment-naive and pretreated adolescents with HIV-1 infection aged ≥ 12 to < 18 years. This was justified with a high antiretroviral efficacy and a good tolerability of DOR. In addition, the intake of DOR once daily would contribute to treatment adherence and DOR would offer a high degree of flexibility with regard to the composition of individually tailored free combinations with other drugs, so that a transferability of the results of cohort 2 to DOR in free combination with other antiretroviral drugs could be assumed.

The data presented are unsuitable for deriving an added benefit

The approach of the company to derive an added benefit of DOR in combination with other antiretroviral drugs on the basis of the IMPAACT 2014 study is not appropriate, as there are no data for a comparison with the respective ACT and thus no suitable data for the assessment of the added benefit of DOR in the therapeutic indication.

I 1.4 Results on added benefit

In its dossier, the company presented no suitable data to assess the added benefit of DOR in combination with other antiretroviral drugs in treatment-naive and pretreated adolescents with HIV-1 infection from 12 years of age with a body weight of ≥ 35 kg versus the ACT defined by the G-BA for each of the 2 research questions. For both research questions, this resulted in

no hint of an added benefit of DOR in comparison with the ACT; an added benefit is therefore not proven in either case.

I 1.5 Probability and extent of added benefit

The result of the assessment of the added benefit of DOR in comparison with the ACT is presented in Table 5.

Table 5: DOR – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Treatment-naive adolescents[b] infected with HIV-1[c]	▪ Tenofovir alafenamide + emtricitabine or ▪ abacavir + lamivudine or ▪ abacavir + emtricitabine each in combination with ▫ dolutegravir or ▫ atazanavir/ritonavir or ▫ darunavir/ritonavir or ▫ elvitegravir/cobicistat	Added benefit not proven
2	Pretreated adolescents[b] infected with HIV-1	Individual ART choosing from the approved drugs; under consideration of prior treatment(s) and 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. Presented is the respective ACT specified by the GBA.
b. ≥ 12 years of age and with a body weight of ≥ 35 kg.
c. The HI viruses must not have mutations known to be associated with resistances to the substance class of NNRTI.

ART: antiretroviral therapy; DOR: doravirine; G-BA: Federal Joint Committee; HI: human immunodeficiency; HIV-1: human immunodeficiency virus type 1; NNRTI: non-nucleoside reverse transcriptase inhibitors

The assessment described above deviates from the assessment by the company, which claimed a hint of a non-quantifiable added benefit across both research questions.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-52.html.