IQWiG Reports – Commission No. A22-49

Doravirine/lamivudine/tenofovir disoproxil fumarate (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/Lamivudin/Tenofovirdisoproxilfumarat (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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Doravirine/lamivudine/tenofovir disoproxil fumarate(HIV infection in adolescents) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
29 April 2022

Internal Commission No.
A22-49

Address of publisher
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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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Keywords: Doravirine, Lamivudine, Tenofovir, HIV Infections, Adolescent, Benefit Assessment

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
ACT	appropriate comparator therapy
ART	antiretroviral therapy
DOR/3TC/TDF	doravirine/lamivudine/tenofovir disoproxil fumarate
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
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

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 combination doravirin/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF). 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 29 April 2022.

Research question

The aim of the present report is the assessment of the added benefit of DOR/3TC/TDF 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), whereby 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). In addition, toxicities must have occurred that preclude the use of other treatment regimens without TDF.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of DOR/3TC/TDF

Therapeutic indication	ACT[a]
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 ACT specified by the G-BA.
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, 3TC or tenofovir. In addition, toxicities must have occurred that preclude the use of other treatment regimens without TDF.

3TC: lamivudine; ACT: appropriate comparator therapy; 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; TDF: tenofovir disoproxil fumarate

The company followed the ACT specified by the G-BA.

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/3TC/TDF 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 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). The company used the results of the 43 pretreated adolescents from cohort 2 of the IMPAACT 2014 study to derive the added benefit and derived a hint of a non-quantifiable added benefit of DOR/3TC/TDF for pretreated adolescents with HIV-1 infection aged ≥ 12 to < 18 years on the basis of the non-comparative data on DOR/3TC/TDF.

Thus, in its dossier, the company does not present suitable data to assess the added benefit of DOR/3TC/TDF compared with the ACT in adolescents aged 12 years and older and with a body weight of ≥ 35 kg who are infected with HIV 1, whereby the HIV viruses must not have mutations that are known to be associated with resistances to the substance class of NNRTIs, 3TCs or tenofovir, and who have experienced toxicities that preclude the use of other treatment regimens without TDF. This resulted in no hint of an added benefit of DOR/3TC/TDF in comparison with the ACT; an added benefit is therefore not proven.

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 the drug combination DOR/3TC/TDF.

[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].

Table 3: DOR/3TC/TDF – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
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 ACT specified by the G-BA.
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, 3TC or tenofovir. In addition, toxicities must have occurred that preclude the use of other treatment regimens without TDF.

3TC: lamivudine; 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; TDF: tenofovir disoproxil fumarate

The G-BA decides on the added benefit.

I 1.2 Research question

The aim of the present report is the assessment of the added benefit of DOR/3TC/TDF in comparison with the ACT in adolescents from 12 years of age and with a body weight of ≥ 35 kg, infected with HIV-1, whereby 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). In addition, toxicities must have occurred that preclude the use of other treatment regimens without TDF.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of DOR/3TC/TDF

Therapeutic indication	ACT[a]
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 ACT specified by the G-BA.
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, 3TC or tenofovir. In addition, toxicities must have occurred that preclude the use of other treatment regimens without TDF.

3TC: lamivudine; 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; TDF: tenofovir disoproxil fumarate

The company followed the ACT specified by the G-BA.

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/3TC/TDF (status: 08 March 2022)
- bibliographical literature search on DOR/3TC/TDF (last search on 9 March 2022)
- search in trial registries for studies on DOR/3TC/TDF (last search on 1 March 2022)
- search on the G-BA website for DOR/3TC/TDF (last search on 9 March 2022)

To check the completeness of the study pool:

- search in trial registries for studies on DOR/3TC/TDF (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/3TC/TDF versus the ACT.

In its dossier, the company presents data of the single-arm study IMPAACT 2014 [3-6] under "further studies" 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 studies" is not suitable for deriving an added benefit of DOR/3TC/TDF 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 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, orally, as a single dose in addition to their ongoing ART (consisting of 1 integrase inhibitor and 2 nucleoside reverse transcriptase inhibitors [NRTIs]) to investigate

pharmacokinetics and safety until day 14. Patients from cohort 1 were allowed to switch to cohort 2.

Patients in cohort 2 received the fixed combination DOR/3TC/TDF orally once daily for 96 weeks according to the Summary of Product Characteristics (SPC) [7]. 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 adolescents in cohort 2; according to the inclusion criteria, resistance testing was not mandatory for the participation in the study. Moreover, the therapeutic indication of DOR/3TC/TDF covers adolescents who had experienced toxicities which excluded the use of other treatment regimens without TDF [7]. This was no prerequisite for the participation in IMPAACT 2014. Overall, 19 of 43 adolescents (44%) had received a regiment with TDF before being included in the study. For these patients, it is unclear whether other therapy regimens without TDF were excluded due to toxicities. For the remaining patients, it is assumed that therapy regimens without TDF were also eligible, since according to the inclusion criteria, the previous ART could not have been changed due to clinical or virological therapy failure and the available study documents did not suggest that a treatment switch due to side effects was indicated. 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

Under "further studies" in Module 4 A of the dossier, the company presents the results of cohort 2 both separately by the treatment status (treatment-naive, pretreated) and descriptively for the entire cohort 2. The results included data on the efficacy at week 48 (last patient visit: 20 January 2021) as well as results on the 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.

The company used the results of the pretreated adolescents from cohort 2 of the IMPAACT 2014 study to derive the added benefit and derived a hint of a non-quantifiable added benefit of DOR/3TC/TDF for 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/3TC/TDF. Moreover, taking the fixed combination once daily would contribute to treatment adherence.

The data presented are unsuitable for deriving an added benefit

The approach of the company to derive an added benefit of DOR/3TC/TDF on the basis of the subpopulation of pretreated adolescents from cohort 2 of the IMPAACT 2014 study described in the previous section is not appropriate, as there are no data for a comparison with the ACT and thus no suitable data for the assessment of the added benefit of DOR/3TC/TDF in the therapeutic indication.

I 1.4 Results on added benefit

In its dossier, the company does not present suitable data to assess the added benefit of DOR/3TC/TDF compared with the ACT in adolescents aged 12 years and older and with a body weight of ≥ 35 kg who are infected with HIV 1, whereby the HIV viruses must not have mutations that are known to be associated with resistances to the substance class of NNRTIs, 3TCs or tenofovir, and who have experienced toxicities that preclude the use of other treatment regimens without TDF. This resulted in no hint of an added benefit of DOR/3TC/TDF in comparison with the ACT; an added benefit is therefore not proven.

I 1.5 Probability and extent of added benefit

The result of the assessment of the added benefit of DOR/3TC/TDF in comparison with the ACT is presented in Table 5.

Table 5: DOR/3TC/TDF – probability and extent of added benefit:

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
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 ACT specified by the G-BA.
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, 3TC or tenofovir. In addition, toxicities must have occurred that preclude the use of other treatment regimens without TDF.

3TC: lamivudine; 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; TDF: tenofovir disoproxil fumarate

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit in the present therapeutic indication on the basis of the pretreated adolescents from cohort 2 of the IMPAACT 2014 study.

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/a22-49.html.