IQWiG Reports – Commission No. A18-34

Dolutegravir/rilpivirine (HIV infection) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Dolutegravir/Rilpivirin (HIV-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 September 2018). Please note: This document was translated by an external translator and 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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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 dolutegravir/rilpivirine (DTG/RPV). 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 24 May 2018.

Research question

The aim of this report is to assess the added benefit of DTG/RPV in comparison with individualized antiretroviral therapy (ART) as the appropriate comparator therapy (ACT) in adult patients infected with human immunodeficiency virus type 1 (HIV-1) who are virologically suppressed (< 50 HIV-1 ribonucleic acid [RNA] copies/ml), have been on a stable regimen for at least 6 months, and have no past virologic failure and no known or suspected resistances against non-nucleoside reverse transcriptase inhibitors (NNRTI) or integrase inhibitors (INI).

The G-BA's specification of the ACT resulted in one research question, which is presented in Table 2 below.

Table 2[2]: Research questions of the benefit assessment of dolutegravir/rilpivirine

Indication	ACT[a]
Adults infected with human immunodeficiency virus type 1 who are virologically suppressed (<50 HIV-1 RNA copies/ml), have been on a stable regimen for ≥6 months and have no past virologic failure and no known or suspected resistances to NNRTIs or INIs.	Individualized antiretroviral therapy based on the prior therapy/therapies and under consideration of any adverse events[b]
a: Presentation of the respective ACT specified by the G-BA. b: For patients without indication for a treatment switch, the existing therapy should be continued in the comparator arm. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1; human immunodeficiency virus type 1; INI: integrase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid	

The company followed the G-BA's specification of the ACT.

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 deriving the added benefit. This corresponds to the company's inclusion criteria.

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

Results

For adults infected with human immunodeficiency virus type 1 who are virologically suppressed (< 50 HIV-1 RNA copies/ml), have been on a stable regimen for ≥ 6 months, and have no past virologic failure and no known or suspected resistances to NNRTIs or INIs, the two studies SWORD-1 and SWORD-2 were included in the benefit assessment.

Study design

The studies SWORD-1 and SWORD-2 included almost exclusively patients without indication for a treatment switch (e.g. due to adverse events). The studies SWORD-1 and SWORD-2 were therefore used to draw conclusions about this patient group only. No studies were available on pretreated adults with indication for a treatment switch.

SWORD-1 and SWORD-2 are open-label, parallel-group RCTs with identical design. Both studies examined pretreated HIV-1-infected adults who were virologically suppressed (< 50 HIV-1 RNA copies/ml), had been on a stable regimen for ≥ 6 months, and had no past virologic failure and no known or suspected resistance to NNRTIs or INIs. In the studies, DTG/RPV was compared with continuation of the existing therapy consisting of 2 nucleoside reverse transcriptase inhibitors (NRTI) and a 3rd combination partner (NNRTI, protease inhibitor [PI] or an INI). The study drug was administered in accordance with the Summary of Product Characteristics (SPC) (i.e. in accordance with the local SPC in the studies' comparator arms).

The primary outcome of both studies was virologic response (HIV-1 RNA < 50 copies/ml). Other patient-relevant outcomes were mortality, morbidity, and adverse events (AEs). Data on health-related quality of life were not collected in either study.

The assessment is based on the data cut-off date of the Week-48 analysis.

Implementation of the ACT in the studies SWORD-1 and SWORD-2

The content-related review of the examined patient population showed that the studies SWORD-1 and SWORD-2 predominantly included patients without medically necessary indication for a treatment switch.

For adults without indication for a treatment switch, continuation of the existing individualized therapy is considered the adequate implementation of the ACT specified by the G-BA in the control arms of the studies SWORD-1 and SWORD-2.

Risk of bias

The risk of bias on the study level is assessed as low for both studies.

The risk of bias of the results of the outcomes all-cause mortality, AIDS-defining events (Centers for Disease Control and Prevention [CDC] Category C), virologic response, virologic failure, Cluster-of-Differentiation-4-positive ($CD4^+$) cell count, serious adverse events (SAEs)

and severe adverse events (AE) (Division of AIDS [DAIDS] Grade 3–4) is considered low. For the outcomes HIV-associated events, HIV symptom index (HIV-SI) (Symptom Bother Score), health status (European Quality of Life [EQ-5D], Visual Analogue Scale [VAS]), discontinuation due to AEs and the specific AEs, the risk of bias of the results is rated as high. On the basis of the available data, at most proof can be derived from the results of outcomes with low risk of bias, and at most indications, e.g. of added benefit, can be derived for the results of all other outcomes due to the high risk of bias.

Results

Mortality

- Overall survival

For the outcome overall survival, the meta-analysis of the SWORD-1 and SWORD-2 studies does not show a statistically significant difference between treatment groups. Consequently, there is no hint of added benefit of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI). An added benefit is therefore not proven.

Morbidity

- AIDS-defining events (CDC Category C) and supplementary consideration of the outcomes virologic response, virologic failure and $CD4^+$ cell count

The meta-analysis shows no statistically significant difference between treatment groups for the outcome AIDS-defining events (CDC Category C) or the additionally presented outcomes virologic response, virologic failure, and $CD4^+$ cell count. Overall, there is consequently no hint of added benefit of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI); an added benefit is therefore not proven.

- HIV-associated events (CDC Category B)

For the outcome HIV-associated events (CDC Category B events), the meta-analysis shows no statistically significant difference between treatment groups. Consequently, there is no hint of added benefit of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI); an added benefit is therefore not proven.

- Health status as measured by EQ-5D VAS

For the outcome health status, as measured by EQ-5D VAS, the meta-analysis shows no statistically significant difference between treatment groups. Consequently, there is no hint of added benefit of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI); an added benefit is therefore not proven.

- Symptoms measured by the HIV-SI (Symptom Bother Score)

For the outcome HIV-SI (Symptom Bother Score), the meta-analysis shows a statistically significant difference in favour of DTG/RPV. The 95% confidence interval (CI) of the standardized mean difference (Hedges' g) is, however, not fully outside of the irrelevance range of −0.2 to 0.2. Hence, the effect cannot be rated as relevant. Consequently, there is no hint of added benefit of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI); an added benefit is therefore not proven.

Health-related quality of life

In the SWORD-1 and SWORD-2 studies, no outcomes from the outcome category health-related quality of life were investigated. Consequently, there is no hint of added benefit of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI); an added benefit is therefore not proven.

Adverse events

- SAEs and severe AEs (DAIDS grade 3–4)

For the outcomes SAEs and severe AEs (DAIDS Grade 3–4), the meta-analysis shows no statistically significant difference between treatment groups. Consequently, there is no hint of greater or lesser harm of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI). Greater or lesser harm is therefore not proven.

- Discontinuation due to AEs

For the outcome discontinuation due to AEs, the meta-analysis shows a statistically significant difference to the disadvantage of DTG/RPV. Events leading to discontinuation due to AEs in the DTG/RPV arm were largely AEs of the System Organ Class (SOC) psychiatric disorders and the SOC gastrointestinal disorders (see Table 23 and Table 24 of the full dossier assessment). This is consistent with the results for the specific AEs psychiatric disorders and gastrointestinal disorders, each of which showing one statistically significant result to the disadvantage of DTG/RPV (see below). Consequently, there is a hint of greater harm of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI).

- Specific AEs
  - Gastrointestinal disorders, disorders of the nervous system, and psychiatric disorders

For each of the outcomes gastrointestinal disorders, disorders of the nervous system, and psychiatric disorders, the meta-analysis shows a statistically significant difference to the disadvantage of DTG/RPV. For each of them, there is consequently an indication of greater harm of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI).

- Diseases of the skin and subcutaneous tissue

For the outcome skin and subcutaneous tissue disorders, the meta-analysis shows a statistically significant difference to the disadvantage of DTG/RPV. Furthermore, an effect modification by the attribute $CD4^+$ cell count was found for this outcome. For patients with a $CD4^+$ cell count of < 500 cells/µl at the start of the study, there is no hint of greater harm of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI). For patients with a $CD4^+$ cell count ≥ 500 cells/µl at the start of the study, there is an indication of greater harm of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI).

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

On the basis of the results presented, the probability and extent of the added benefit of the drug DTG/RPV in comparison with the ACT is assessed as follows:

Overall, for negative effects, there are several indications of greater harm of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI). The extent of some of the negative effects was classified as considerable.

In summary, for pretreated HIV-1-infected adults who are virologically suppressed (HIV-1 RNA < 50 copies/ml), have been on a stable regimen for at least 6 months, and have no past virologic failure, no known or suspected resistances to NNRTIs or INIs and no indication for a treatment switch, there is an indication of lesser benefit of DTG/RPV in comparison with continuation of the existing therapy consisting of 2 NRTIs and a 3rd combination partner (NNRTI, PI, or INI).

The company did not present any data on pretreated HIV-1-infected adults who are virologically suppressed (HIV-1 RNA < 50 copies/ml), have been on a stable regimen for at least 6 months, and have no past virologic failure, no known or suspected resistances to NNRTIs or INIs and no indication for a treatment switch. For this population, there is no hint of added benefit; an added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of the added benefit of DTG/RPV.

[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: Dolutegravir/rilpivirine – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Adults infected with human immunodeficiency virus type 1 who are virologically suppressed (<50 HIV-1 RNA copies/ml), have been on a stable regimen for ≥6 months, and have no past virologic failure and no known or suspected resistances to NNRTIs or INIs.	Individualized antiretroviral therapy based on the prior therapy/therapies and under consideration of any adverse events[b]	
Without indication for a treatment switch		Indication of lesser benefit
With indication for a treatment switch		Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: For patients without indication for a treatment switch, the existing therapy should be continued in the comparator arm. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1; human immunodeficiency virus type 1; INI; integrase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. 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 5.0 [online]. 10 July 2017 [Accessed: 04 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.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/a18-34-dolutegravir-rilpivirine-hiv-infection-benefit-assessment-according-to-35a-social-code-book-v.10098.html.