IQWiG Reports – Commission No. A18-64

Tenofovir alafenamide (chronic hepatitis B) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of the executive summary of the dossier assessment *Tenofoviralafenamid (chronische Hepatitis B) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 20 December 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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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 tenofovir alafenamide (TAF). For the drug to be assessed, the pharmaceutical company (hereinafter referred to as "the company") submitted a dossier for early benefit assessment for the first time on 30 March 2017. It was assessed in benefit assessment A17-13. The validity period of the associated decision had been limited by the G-BA since the data submitted by the company were incomplete in content. After expiry of the decision, the company submitted another dossier, received by IQWiG on 28 September 2018. The assessment is based on the dossier compiled by the company.

Research question

This assessment aims to assess the added benefit of TAF in comparison with the appropriate comparator therapy (ACT) in adults and adolescents (aged 12 years or above and of a body weight of at least 35 kg) for the treatment of chronic hepatitis B.

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

Table 2[2]: Research questions of the benefit assessment of TAF in chronic hepatitis B

Research question	Indication	ACT[a]
1	Treatment-naïve adults	(PEG-)Interferon alfa or tenofovir disoproxil or entecavir
2	Pretreated adults	Individualized ART depending on prior treatment(s) and under consideration of the reason for switching the treatment, particularly treatment failure due to virologic failure and any accompanying development of resistance or due to adverse events
3	Treatment-naïve adolescents[b]	Tenofovir disoproxil or entecarvir
4	Pretreated adolescents[b]	Tenofovir disoproxil

a: Presentation of the respective ACT specified by the G-BA.
b: Aged 12 years or above and of a body weight of at least 35 kg.
ACT: appropriate comparator therapy; ART: antiretroviral therapy; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide

The company followed the G-BA's specification of the ACT for all research questions.

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

The assessment was conducted using 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 deriving any added benefit. This coincides with the company's inclusion criteria.

Results

Research question 1: treatment-naïve adults

Study pool and study characteristics

The benefit assessment of TAF in treatment-naïve adults included the studies GS 108, GS 108-C, GS 110, and GS 110-C.

GS 108, GS 108-C, GS 110, and GS 110-C are 4 randomized, double-blind parallel-group studies with nearly identical study design. The main difference between the 4 studies is that the GS 108 and GS 108-C studies were conducted in patients with negative hepatitis B-e antigen (HBeAg) status, while GS 110 and GS 110-C included only patients with positive HBeAg status. GS 108-C and GS 100-C each concerned additional cohorts to the respective main studies; said add-on studies included only patients in China and were planned only after the main studies had started. Otherwise, the inclusion criteria of all 4 studies were nearly identical. All 4 studies included adult patients with documented chronic hepatitis B infection (e.g. hepatitis B surface antigen [HBsAg]-positive for more than 6 months).

The 4 studies included a total of 1637 patients and randomized them in a 2:1 ratio to treatment with either TAF (N = 1095) or tenofovir disoproxil fumarate (TDF) (N = 542). In both study arms, treatment was performed in accordance with the respective Summary of Product Characteristics (SPC).

The primary outcome of all 4 studies was virologic response. Patient-relevant secondary outcomes were all-cause mortality , the occurrence of hepatocellular carcinomas, and adverse events (AEs).

Relevant subpopulation

For the present research question 1 (treatment-naïve adults), the subpopulation of 1090 treatment-naïve adults without any pretreatment is relevant for all 4 studies (TAF: N = 727; TDF: N = 363). The company submitted the corresponding analyses in the dossier.

Data cut-offs

For the benefit assessment regarding treatment-naïve adults, data at the 96-week data cut-off are used for all 4 studies.

Risk of bias

The risk of bias at study level is rated as low for all 4 studies (GS 108, GS 108-C, GS 100, and GS 110-C). The risk of bias at outcome level is rated as low for all outcomes as well.

Results

Mortality

- All-cause mortality

No death occurred in the 4 studies GS 108, GS 108-C, GS 110, and GS 110-C. Consequently, there is no hint of added benefit of TAF in comparison with tenofovir disoproxil; an added benefit is therefore not proven.

Morbidity

- Hepatocellular carcinoma

For the outcome of hepatocellular carcinoma, only few events occurred in the 4 studies GS 108, GS 108-C, GS 110, and GS 110-C: in the TAF-arms, 3 events (0.4%) and in the TDF arms, 5 events (1.4%). In the metaanalysis of the 4 studies, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of TAF in comparison with tenofovir disoproxil; an added benefit is therefore not proven.

- Hepatic cirrhosis

For the outcome of hepatic cirrhosis, no usable data were available. Consequently, there is no hint of added benefit of TAF in comparison with tenofovir disoproxil; an added benefit is therefore not proven.

Health-related quality of life

In the studies GS 108, GS 108-C, GS 110, and GS 110-C, no outcomes from the outcome category of health-related quality of life were examined. Consequently, there is no hint of added benefit of TAF in comparison with tenofovir disoproxil; an added benefit is therefore not proven.

Adverse events

- SAEs, severe AEs (GSI scale grades 3 to 4), and discontinuation due to AEs

For each of the outcomes of SAEs, severe AEs (GSI scale grades 3 to 4), and discontinuation due to AEs, the metaanalysis of the 4 studies GS 108, GS 108-C, GS 110, and GS 110-C shows no statistically significant difference between treatment groups. Consequently, none of the studies result in a hint of greater or lesser harm of TAF in comparison with tenofovir disoproxil; greater or lesser harm is therefore not proven for these outcomes.

- Diseases of the kidney and urinary tract as well as bone fractures

For each of the specific AEs of diseases of the kidney and urinary tract as well as bone fractures, the metaanalysis of the 4 studies GS 108, GS 108-C, GS 110, and GS 110-C shows no statistically significant difference between treatment groups. Consequently, none of the studies result in a hint of greater or lesser harm of TAF in comparison with tenofovir disoproxil; greater or lesser harm is therefore not proven for these outcomes.

- Other specific AEs

For this assessment, no other specific AEs were found which would allow for greater or lesser harm of TAF to be inferred. Consequently, there is no hint of greater or lesser harm of TAF in comparison with tenofovir disoproxil; greater or lesser harm is therefore not proven.

Results of the benefit assessment from subgroups

Regarding the included patient-relevant outcomes, no relevant subgroup results were found.

Research questions 2, 3, and 4: pretreated adults as well as treatment-naïve and pretreated adolescents

No relevant data are available to assess the added benefit of TAF in comparison with the ACT in pretreated adults as well as treatment-naïve and pretreated adolescents with chronic hepatitis B. This results in no hint of an added benefit of TAF in comparison with the ACT for research questions 2, 3, and 4 (pretreated adults as well as treatment-naïve and pretreated adolescents); an added benefit is therefore not proven.

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 added benefit of the drug TAF in comparison with the ACT is assessed as follows:

For treatment-naïve adults with chronic hepatitis B, neither positive nor negative effects were found. Consequently, there is no hint of added benefit of TAF in comparison with tenofovir disoproxil for this patient group; an added benefit is not proven.

For all other research questions (pretreated adults as well as pretreated and treatment-naïve adolescents), no relevant data are available. For these patients as well, 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 added benefit of TAF.

[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: TAF – Probability and extent of added benefit in chronic hepatitis B

Indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment-naïve adults	(PEG-)Interferon alfa or tenofovir disoproxil or entecavir	Added benefit not proven
Pretreated adults	Individualized ART depending on prior treatment(s) and under consideration of the reason for switching the treatment, particularly treatment failure due to virologic failure and any accompanying development of resistance or due to adverse events	Added benefit not proven
Treatment-naïve adolescents[b]	Tenofovir disoproxil or entecarvir	Added benefit not proven
Pretreated adolescents[b]	Tenofovir disoproxil	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: Aged 12 years or above and of a body weight of at least 35 kg. ACT: appropriate comparator therapy; ART: antiretroviral therapy; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide		

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: 4 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/a18-64-tenofovir-alafenamide-chronic-hepatits-b-benefit-assessment-according-to-35a-social-code-book-v.10625.html.