IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Tafluprost/timolol (Addendum to Commission A14-49)[1]

Addendum

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Version: 1.0
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[1] Translation of addendum A15-19 *Tafluprost/Timolol* (*Addendum zum Auftrag A14-49*) (Version 1.0; Status: 29 May 2015). 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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Keywords: tafluprost, timolol, glaucoma – open-angle, ocular hypertension, benefit assessment

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

Table of contents

List of abbreviations

Abbreviation	Meaning
AE	adverse event
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 26 May 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-49 (*Tafluprost/timolol – Benefit assessment according to §35a SGB V* [1]).

With its comment, the pharmaceutical company (hereinafter referred to as "the company") presented further analyses on the 201051 study on the comparison of the fixed-dose combination of tafluprost and timolol (hereinafter referred to as "tafluprost/timolol") with the free combination of these drugs [2]. This study was already contained in the company's dossier [3] and was included as relevant in the dossier assessment A14-49 [1]. The G-BA commissioned IQWiG to assess the documents submitted.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

With its comment, the company presented further analyses on the 201051 study on the comparison of the fixed-dose combination of tafluprost/timolol in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical monotherapy with beta-blockers or prostaglandin analogues and require combination therapy and who would benefit from preservative-free eye drops.

Among other things, the patients in the 201051 study were partly treatment-naive and therefore did not comply with the approved population. However, the company presented the results of the total population of the study in Module 4A of the dossier. Subgroup analyses provided analyses evaluable for dossier assessment A14-49 only for those patients who had received pretreatment with prostaglandin analogues as monotherapy at study inclusion. These analyses, which only covered part of the approved therapeutic indication, were assessed as having an increased risk of bias because the results of a total of 58 patients were lacking in relation to the total study, and it was unclear how these were distributed among the different subgroups after pretreatment [1].

The analyses subsequently submitted by the company with the comment were presented separately for patients with previous beta-blocker monotherapy, prostaglandin analogue monotherapy, and beta-blocker or prostaglandin analogue monotherapy. According to the company, these analyses include patients who had the pretreatments mentioned in the course of the last 2 years prior to the start of the study. The new analyses of the company included the following outcomes: ocular surface disease, visual field defects, visual acuity (improvement and worsening), adverse events (AEs), serious adverse events (SAEs), discontinuation due to AEs, as well as ocular AEs, ocular SAEs and discontinuation due to ocular AEs.

The analyses subsequently submitted by the company were not evaluable because they contained several incomprehensible inconsistencies. On page 20 of its comment, the company provided a presentation of the patients by pretreatments [2] aiming to dissolve the uncertainty regarding the 58 missing patients described above. It also described that the data submitted with its comment refer to pretreatments in the course of the last 2 years. The dossier also contained data on pretreatments of the last 2 years (see Module 4A, Table 4-14, and dossier assessment, Table 6). It is notable that the information in the dossier (including the clinical study report [CSR]) contained multiple answers, i.e. some patients had received several pretreatments in the last 2 years. However, the data in the comment did not contain multiple answers (the numbers for each pretreatment add up to the sum of randomized patients). As a result, the information in the comment appeared inconsistent. The data are not plausible and can also not be comprehended using the CSR. Since the distribution of groups by pretreatment followed a different categorization in the comment than in the dossier, the differences cannot be comprehended.

Moreover, the data in the comment partly did not concur with the ones in the dossier. The number of treatment-naive patients is an example of these inconsistent data. The number of treatment-naive patients for the time period of the last 2 years in the comment (intervention: N = 63, control: N = 54) did not concur with the information provided in the dossier for the same period of time (N = 63 versus N = 56), but with the data in the dossier on the time point of screening (with the missing 58 patients described above). It is unclear whether this inconsistency was due to an incorrect categorization or to patients missing in the presentation. It cannot be clarified on the basis of the available information whether this also applied to further patients. Moreover, the data on patient characteristics in the documents subsequently submitted were partly based on incomprehensible patient numbers. These numbers neither concurred with the patient numbers on pretreatment mentioned in the comment nor with the ones in the result tables on outcomes subsequently submitted. Overall, the data subsequently submitted contained several inconsistencies, which in total raise doubts about the validity of the data submitted. The data are therefore not evaluable.

Besides the inconsistencies in patient numbers described above, it is doubtful whether the data provided by the company in the comment comprise the relevant population according to the research question of the benefit assessment. According to the approval of the fixed-dose combination of tafluprost/timolol [4], the therapeutic indication comprises patients pretreated with monotherapy with beta-blockers or prostaglandin analogues and require combination therapy. For the dossier assessment on Commission A14-49 [1], analyses were available on those patients who had been pretreated with a prostaglandin analogue in monotherapy at the time point of the start of the study [3]. These were considered relevant for the dossier assessment. Patients who had received monotherapy with a beta-blocker or prostaglandin analogue in the course of the last 2 years before the start of the study may also have received combination therapy in this period. The proportion of these patients in the 201051 study was not clear from the information in the dossier or from the company’s comment. It remains questionable whether the approval of tafluprost/timolol also applies to patients who have already received combination therapy because the approval does not mention substitution of a combination therapy.

3 Summary

Due to the accumulation of several incomprehensible inconsistencies, the data subsequently submitted by the company are not evaluable for the benefit assessment. Hence they do not change the conclusion of dossier assessment A14-49. Even if it was possible to consider them for the benefit assessment, they would not change the conclusion of dossier assessment A14-49 because none of the new analyses presented a result with a statistically significant difference between the treatment groups.

The added benefit of tafluprost/timolol (fixed combination) versus the appropriate comparator therapy (tafluprost + timolol in non-fixed combination) is not proven.

4 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Tafluprost/Timolol: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-49 [online]. 30 March 2015 [accessed: 2 May 2015]. (IQWiG-Berichte; Volume 292). URL: https://www.iqwig.de/download/A14-49_Tafluprost-Timolol_Nutzenbewertung-35a-SGB-V.pdf.

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3. Santen GmbH. Konservierungsmittelfreie Fixdosiskombination (FDK-TT) Tafluprost und Timolol (Taptiqom®); Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 A; Senkung des Augeninnendrucks (IOD) bei erwachsenen Patienten mit Offenwinkelglaukom oder okulärer Hypertension, die auf eine topische Monotherapie mit Betablockern oder Prostaglandinanaloga nur unzureichend ansprechen und eine Kombinationstherapie benötigen, und die von konservierungsmittelfreien Augentropfen profitieren; medizinischer Nutzen und medizinischer Zusatznutzen; Patientengruppen mit therapeutisch bedeutsamen Zusatznutzen. 2015.

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