IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Tafluprost/timolol – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Tafluprost/Timolol – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 March 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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Address of publisher:
Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Daniela Claessens, Ophthalmological Group Practice, Cologne, Germany

IQWiG thanks the medical and scientific advisor for her 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.

IQWiG employees involved in the dossier assessment[2]:

- Teresa Labahn
- Katharina Biester
- Andreas Gerber-Grote
- Wolfram Groß
- Gloria Hanke
- Corinna Kiefer
- Marco Knelangen
- Beate Wieseler

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.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IOP	intraocular pressure
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
OSD	ocular surface disease
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 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 tafluprost/timolol. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 22 December 2014.

Research question

The aim of the present report was to assess the added benefit of the drug combination tafluprost/timolol in comparison with the appropriate comparator therapy (ACT) 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.

The G-BA specified a combination therapy of beta-blocker + prostaglandin analogue or beta-blocker + prostamide as non-fixed or fixed combination as ACT. The company chose the combination of beta-blocker + prostaglandin analogue.

For the benefit assessment, the company presented a study on the comparison of the fixed combination of tafluprost and timolol with the non-fixed combination of the same drugs. On the basis of the specification of the ACT, this comparison is possible.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier.

Results

One relevant study (Study 201051) was available for the benefit assessment. This was a randomized, active-controlled, double-blind, multicentre study, in which the fixed combination of tafluprost and timolol (hereinafter: "tafluprost/timolol") was compared with the non-fixed combination of the two individual agents tafluprost and timolol (hereinafter: "tafluprost + timolol"). Adult patients diagnosed with either open-angle glaucoma or ocular hypertension in one or both eyes who, according to the inclusion criteria of the study, had a need for an additional intraocular pressure (IOP)-lowering medication were enrolled. It was clear from the study documents that treatment-naive patients could also be enrolled. Screening was followed by a washout-phase, which depended on the previous medical glaucoma treatment (5 days to 4 weeks). The treatment duration was 6 months.

Patients with different pretreatments and treatment-naive patients were enrolled in the study. The subpopulation of the study that comprised patients with previous monotherapy with beta-blockers or prostaglandin analogues is relevant for the present benefit assessment. This is

determined by the therapeutic indication of tafluprost/timolol. A total of 400 patients were randomly assigned to the 2 study arms, 201 of these patients to the tafluprost/timolol arm, and 199 to the tafluprost + timolol arm. No information was available on the size of the relevant subpopulation of patients with previous monotherapy with beta-blockers or prostaglandin analogues. The proportion of the relevant subpopulation of Study 201051 available for the benefit assessment (pretreatment with prostaglandin analogue monotherapy; hereinafter: "available population") resulted from subgroup analyses after pretreatment with IOP-lowering medication and corresponds to the subgroup of patients who were pretreated with monotherapy with prostaglandin analogues. It consisted of 69 patients.

The primary outcome recorded in Study 201051 was the change in IOP. Patient-relevant secondary outcomes were change in visual acuity, visual field defects and adverse events.

No information on patient characteristics was available for the available population of patients who were pretreated with monotherapy with prostaglandin analogues.

Risk of bias

The risk of bias of Study 201051 was rated as high at study level and for all patient-relevant outcomes for which the dossier contained evaluable data. It cannot be excluded that the intention to treat (ITT) principle for the available population of patients pretreated with prostaglandin analogue monotherapy was violated. No subgroup analysis was conducted for a total of 58 of the 400 (14.5%) randomized patients in the study after previous treatment with IOP-lowering medication, from which the population available for the benefit assessment resulted. There was no information about how these 58 patients were distributed among the corresponding subgroups or how many of these patients would have to be categorized as the subgroup "prostaglandin analogue monotherapy". It therefore remains unclear how large the actual proportion of patients for the available population is. The risk of bias was not estimated for the outcomes on ocular surface disease (OSD), visual acuity and visual field defects and on health-related quality of life because no (evaluable) data were available.

Mortality

Information on deaths was available for Study 201051. No deaths occurred during the total study duration. There is no hint of an added benefit of tafluprost/timolol in comparison with tafluprost + timolol for this outcome, an added benefit is therefore not proven.

Morbidity

Ocular surface disease

There were no evaluable data for the outcome "OSD" because there are doubts about the patient relevance of the operationalization presented. There is no hint of an added benefit of tafluprost/timolol in comparison with tafluprost + timolol, an added benefit is therefore not proven.

Improvement or worsening of visual acuity, visual field defects

There were no evaluable data for the available population of patients pretreated with prostaglandin analogue monotherapy for the outcomes "improvement or worsening of visual acuity" and "visual field defects". Hence there is no hint of an added benefit of tafluprost/timolol in comparison with tafluprost + timolol for these outcomes, an added benefit is not proven.

Health-related quality of life

Health-related quality of life was not investigated in the study. There is no hint of an added benefit of tafluprost/timolol in comparison with tafluprost + timolol for this outcome, an added benefit is therefore not proven.

Adverse events

Overall rate of serious adverse events (SAEs), discontinuation due to adverse events (AEs), ocular AEs, ocular SAEs, discontinuation due to ocular AEs

There was no statistically significant difference between the 2 treatment groups for the outcomes "SAEs" and "ocular AEs". There were no discontinuations due to AEs (and hence also no discontinuations due to ocular AEs) or ocular SAEs. There is no hint of greater or lesser harm of tafluprost/timolol versus tafluprost + timolol, greater or lesser harm is therefore not proven for any of the outcomes mentioned above.

Subgroups and other effect modifiers

No subgroup analyses were available for the available population of patients who were pretreated with prostaglandin analogue monotherapy.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug combination tafluprost/timolol compared with the ACT is assessed as follows:

Based on the available data there is no proof of added benefit of tafluprost/timolol (fixed combination) in comparison with tafluprost + timolol (non-fixed combination). Overall, neither positive nor negative effects remain for tafluprost/timolol for the population of patients available for the benefit assessment who were pretreated with prostaglandin analogue

[4] 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), see [1]. 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, no added benefit, or less benefit), see [2].

monotherapy. There was no information on patients pretreated with beta-blocker monotherapy.

In summary, the added benefit of tafluprost/timolol (fixed combination) versus the ACT (tafluprost + timolol in non-fixed combination) is not proven.

Table 2 presents a summary of the extent and probability of the added benefit of tafluprost/timolol.

Table 2: Tafluprost/timolol – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Lowering of the IOP 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	Combination therapy of **beta-blocker + prostaglandin analogue** or beta-blocker + prostamide as non-fixed or fixed combination	Added benefit not proven[b]
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: Data were available for patients with previous prostaglandin analogue monotherapy; no data for the benefit assessment were available for patients with previous beta-blocker monotherapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IOP: intraocular pressure		

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of the drug combination tafluprost/timolol in comparison with the ACT 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 [3].

The G-BA specified a combination therapy of beta-blocker + prostaglandin analogue or beta-blocker + prostamide as non-fixed or fixed combination as ACT. The company chose the combination of beta-blocker + prostaglandin analogue.

For the benefit assessment, the company presented a study on the comparison of the fixed combination of tafluprost and timolol with the non-fixed combination of the same drugs. On the basis of the specification of the ACT, this comparison is possible.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier.

2.3 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 tafluprost/timolol (studies completed up to 4 December 2014)
- bibliographical literature search on tafluprost/timolol (last search on 18 November 2014)
- search in trial registries for studies on tafluprost/timolol (last search on 26 November 2014)

To check the completeness of the study pool:

- bibliographical literature search on tafluprost/timolol (last search on 14 January 2015)
- search in trial registries for studies on tafluprost/timolol (last search on 14 January 2015)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: tafluprost/timolol vs. tafluprost + timolol

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
201051	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool concurred with the study pool of the company; however, the present benefit assessment deviated from the company's approach insofar as not the total population of Study 201051 was considered relevant for the present research question. The company, in contrast, used the total study population for its benefit assessment (see Section 2.3.2 and Section 2.7.2.4.1 of the full benefit assessment).

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

Table 4 and Table 5 describe the study used for the benefit assessment.

Table 4: Characteristics of the study included – RCT, direct comparison: tafluprost/timolol vs. tafluprost + timolol

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
201051	RCT, double-blind, active-controlled, parallel	Adult patients diagnosed with either open-angle glaucoma[b] or ocular hypertension in one or both eyes with a clinical need for an (additional)[c] IOP-lowering medication[d,e]	Tafluprost/timolol (N = 201) tafluprost + timolol (N = 199) Relevant subpopulation according to approval: ▪ patients pretreated with monotherapy with beta-blocker or prostaglandin analogue: ND ▫ thereof available population of patients pretreated with prostaglandin analogue monotherapy: n = 69[f]	Screening: ND Washout period[g]: 5 days to 4 weeks depending on previous medication Treatment phase: 6 months	35 study centres in 7 countries (Austria, Bulgaria, Czech Republic, Hungary, Latvia, Portugal, Spain) 3/2011–5/2012	Primary: change of IOP from baseline at the time point 6 months (mean diurnal IOP) Secondary: visual acuity, visual field defects, adverse events

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Patients with the following diagnoses were enrolled: primary open-angle glaucoma, pseudoexfoliative glaucoma, pigmentary glaucoma.
c: Described as "additional" in the inclusion criteria; it was clear from the study documents that treatment-naive patients could also be enrolled.
d: Based on the investigator's opinion.
e: IOP of ≥ 23 mmHg in one or both eyes at the time of the examination at baseline; patients with an IOP of > 36 mmHg at screening or at baseline were excluded from study participation.
f: This population is based on subgroup analyses after pretreatment with IOP-lowering medication. No analysis was conducted for 58 of the 400 randomized patients (14.5%) after such pretreatment. It remains unclear how many of these 58 patients would have to be categorized as the subgroup "prostaglandin analogue monotherapy".
g: In case of previous medical glaucoma treatment.
IOP: intraocular pressure; N: number of randomized patients; n: available population; ND: no data; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: tafluprost/timolol vs. tafluprost + timolol

Study	Intervention	Comparison	Concomitant medication
201051	In the affected eye(s) for 6 months: ▪ once daily, 8:10 AM: tafluprost/timolol[a] (0.0015%/0.5%) ▪ twice daily, 8:00 AM and 8:00 PM: vehicle for timolol	In the affected eye(s) for 6 months: ▪ once daily, 8:10 AM: tafluprost[b] (0.0015%) ▪ twice daily, 8:00 AM and 8:00 PM: timolol[b] (0.5%)	Prohibited medication: ▪ Medication that might have an important influence on the IOP or the study results: including (but not limited to) systemic or topical medication to reduce IOP and corticosteroids
a: Preservative-free fixed combination. b: Preservative-free individual agent. IOP: intraocular pressure; RCT: randomized controlled trial; vs.: versus			

Study 201051 was a randomized, active-controlled, double-blind, multicentre study, in which the fixed combination of tafluprost and timolol (hereinafter: "tafluprost/timolol") was compared with the non-fixed combination of the two individual agents tafluprost and timolol (hereinafter: "tafluprost + timolol"). Adult patients diagnosed with either open-angle glaucoma or ocular hypertension in one or both eyes who had a need for an additional IOP-lowering medication were enrolled. It was clear from the study documents that treatment-naive patients could also be enrolled. Screening was followed by a washout-phase, which depended on the previous medical glaucoma treatment (5 days to 4 weeks). The treatment duration was 6 months.

Patients with different pretreatments and treatment-naive patients were enrolled in the study (see Table 6). The subpopulation of the study that comprised patients with previous monotherapy with beta-blockers or prostaglandin analogues is relevant for the present benefit assessment. This is determined by the therapeutic indication of tafluprost/timolol (see Section 2.2 and Section 2.7.2.4.1 of the full dossier assessment).

A total of 400 patients were randomly assigned to the 2 study arms, 201 of these patients to the tafluprost/timolol arm, and 199 to the tafluprost + timolol arm. No information was available on the size of the relevant subpopulation of patients with previous monotherapy with beta-blockers or prostaglandin analogues. The proportion of the relevant subpopulation of Study 201051 available for the benefit assessment (pretreatment with prostaglandin analogue monotherapy; hereinafter: "available population") resulted from subgroup analyses after pretreatment with IOP-lowering medication and corresponds to the subgroup of patients who were pretreated with monotherapy with prostaglandin analogues ("prostaglandin analogue monotherapy"). It consisted of 69 patients. No analysis by the subgroups mentioned above was conducted for 58 of the 400 randomized patients (14.5%). It remains unclear how many of the 58 patients would have to be categorized as the subgroup "prostaglandin analogue monotherapy".

The fixed combination tafluprost/timolol used in the intervention arm of the study was applied in compliance with the approval. The vehicle of timolol was administered in the intervention arm of the study in the morning and at night to maintain blinding of the study medication versus the comparator arm. In the comparator arm, tafluprost was administered in the morning instead of at night as recommended in the approval. Timolol was used at a drug concentration of 0.5%. The recommendations for the drug concentration of timolol range between 0.1% and 0.5% in the different Summaries of Product Characteristics (SPCs) of timolol; the SPC for the preparation used in the study was not available (see Section 2.7.2.4.1 of the full dossier assessment for details).

The primary outcome recorded in Study 201051 was the change in IOP. Patient-relevant secondary outcomes were change in visual acuity, visual field defects and adverse events.

Table 6 shows the characteristics of the patients in the study included.

No information on patient characteristics was available for the available population of patients who were pretreated with monotherapy with prostaglandin analogues. For this reason, only the corresponding information for the total population of Study 201051 can be presented in Table 6. Hence all conclusions on patient characteristics subsequent to Table 6 can only be drawn for the total population of the study included.

Table 6: Characteristics of the study populations – RCT, direct comparison: tafluprost/timolol vs. tafluprost + timolol

Study **Population** **Characteristics** **Category**	**Tafluprost/timolol** **N = 201**	**Tafluprost + timolol** **N = 199**
201051		
Total study population		
Age [years], mean (SD)	64 (11)	64 (11)
Sex [F/M], %	63/37	61/39
Disease severity (at baseline, visual field testing), n (%)[a]		
normal	100 (49.8[b])	96 (48.2[b])
abnormal/mild	71 (35.3[b])	75 (37.7[b])
abnormal/moderate	27 (13.4[b])	24 (12.1[b])
abnormal/severe	3 (1.5[b])	4 (2.0[b])
Ocular diagnosis (worse eye)[c], n (%)		
none	0 (0)	0 (0)
ocular hypertension	46 (22.9)	44 (22.1)
primary open-angle glaucoma	137 (68.2)	140 (70.4)
pseudoexfoliative glaucoma	15 (7.5)	13 (6.5)
pigmentary glaucoma	3 (1.5)	2 (1.0)
Ocular diagnosis (all eyes), n (%)[d]		
none	10 (2.5)	14 (3.5)
ocular hypertension	99 (24.6)	88 (22.1)
primary open-angle glaucoma	262 (65.2)	273 (68.6)
pseudoexfoliative glaucoma	26 (6.5)	19 (4.8)
pigmentary glaucoma	5 (1.2)	4 (1.0)
Previous IOP medication (last 2 years), n (%)[e]		
prostaglandin analogue monotherapy	75 (37.3)	81 (40.7)
fixed combination with prostaglandin analogue[f]	35 (17.4)	39 (19.6)
other	76 (37.8)	79 (39.7)
ND	1 (0.5)	0 (0)
treatment-naive	63 (31.3[b])	56 (28.1[b])

(continued)

Table 6: Characteristics of the study populations – RCT, direct comparison: tafluprost/timolol vs. tafluprost + timolol (continued)

Study **Population** **Characteristics** **Category**	**Tafluprost/timolol** **N = 201**	**Tafluprost + timolol** **N = 199**
Previous IOP medication (at screening), n (%)[g]		
prostaglandin analogue monotherapy	34 (16.9[b])	35 (17.6[b])
combination therapy with prostaglandin analogue	48 (23.9[b])	49 (24.6[b])
combination therapy without prostaglandin analogue	8 (4.0[b])	7 (3.5[b])
other monotherapy	22 (10.9[b])	22 (11.1[b])
treatment-naive	63 (31.3[b])	54 (27.1[b])
Origin, n (%)		
white	201 (100)	197 (99.0)
black	0 (0)	1 (0.5)
other (Hispanic)	0 (0)	1 (0.5)
Study discontinuations, n (%)	18 (9.0)	9 (4.5)
Available population[h]	**Tafluprost/timolol** n = 34[i]	**Tafluprost + timolol** n = 35[i]
	ND	ND

a: The data were derived from results of the subgroup analyses on disease severity (measured with visual field testing) for the outcomes on AEs. The company did not provide any definition of the categories.
b: Institute's calculation.
c: If both eyes meet the inclusion criteria of the study, the worse eye is the eye with higher IOP at the 8 AM measurement at baseline.
d: The data refer to the total number of eyes and not to the number of patients.
e: Multiple answers possible.
f: In Module 4A of the dossier, the company named this category as preservative-free fixed-dose combination of the individual agents tafluprost and timolol. It is clear from Module 5 of the dossier that the drugs in this category are fixed combinations with prostaglandin analogues – but they include different combinations than the one investigated in this study.
g: The information on previous medication at the time point of screening was derived from the subgroup analyses of the company. No subgroup analysis after pretreatment with IOP-lowering medication was conducted for 58 of the 400 randomized patients (14.5%). It therefore remains unclear how these patients were distributed among the subgroups.
h: Proportion of the relevant subpopulation (pretreatment with prostaglandin analogue monotherapy) available for the benefit assessment.
i: This population is based on subgroup analyses after pretreatment with IOP-lowering medication. No analysis was conducted for 58 of the 400 randomized patients (14.5%) after such pretreatment. It remains unclear how many of these 58 patients would have to be categorized as the subgroup "prostaglandin analogue monotherapy".

AE: adverse event; F: female; IOP: intraocular pressure; M: male; N: number of randomized patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics of the total population at baseline were largely comparable between the 2 treatment arms. Overall more women than men were enrolled in the study. In most patients, ocular diagnosis resulted in primary open-angle glaucoma, approximately one fifth of the patients had ocular hypertension, and fewer than 10% of the patients had secondary open-angle glaucoma (pseudoexfoliative or pigmentary glaucoma). Overall, just under one third of the patients had not been pretreated at the time point of screening for study inclusion; approximately 17% had received monotherapy with a prostaglandin analogue. There was no information on patients with beta-blocker monotherapy insufficient at this time point (see also Section 2.7.2.4.1 of the full dossier assessment). The number of study discontinuations in the tafluprost/timolol arm was twice the number of study discontinuations in the tafluprost + timolol arm (9.0% versus 4.5%).

Table 7 shows the risk of bias at study level.

Table 7: Risk of bias at study level – RCT, direct comparison: tafluprost/timolol vs. tafluprost + timolol

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
201051	Yes	Yes	Yes	Yes	Yes	No[a]	High

a: No analysis after pretreatment with IOP-lowering medication was conducted for 58 of the 400 randomized patients (14.5%). It can therefore not be excluded that the ITT principle for the available population of patients pretreated with prostaglandin monotherapy was violated (see also Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment).

IOP: intraocular pressure; ITT: intention to treat; RCT: randomized controlled trial; vs.: versus

The risk of bias at study level for Study 201051 was rated as high because it cannot be excluded that the ITT principle for the available population was violated. The assessment of the risk of bias deviates from the company's assessment, which assessed the risk of bias at study level as low (see Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment).

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - ocular surface disease
  - improvement of visual acuity
  - worsening of visual acuity
  - visual field defects
- Health-related quality of life
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - ocular AEs
  - ocular SAEs
  - discontinuation due to ocular AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4A), e.g. non-ocular AEs. In addition to the outcomes presented by the company in Module 4A of the dossier, the outcomes "improvement of visual acuity", "worsening of visual acuity" and "visual field defects" were included in the present benefit assessment because they represent additional aspects of morbidity. Reasons for the choice of outcomes are given in Section 2.7.2.4.3 of the full dossier assessment.

Table 8 shows for which outcomes data were available in the study included.

Table 8: Matrix of outcomes – RCT, direct comparison: tafluprost/timolol vs. tafluprost + timolol

Study	Outcomes										
	All-cause mortality	Ocular surface disease	Improvement of visual acuity[a]	Worsening of visual acuity[a]	Visual field defects	Health-related quality of life	SAEs	Discontinuation due to AEs	Ocular AEs	Ocular SAEs	Discontinuation due to ocular AEs
201051	Yes	No[b]	No[b]	No[b]	No[b]	No[c]	Yes	Yes	Yes	Yes	Yes

a: By ≥ 0.2 units on the logMAR scale; equivalent to 10 letters on the ETDRS chart [4].
b: No evaluable data available. See Section 2.7.2.4.3 of the full dossier assessment for reasons.
c: Outcome was not investigated in the study.
AE: adverse event; ETDRS: Early Treatment Diabetic Retinopathy Study; logMAR: logarithm of the minimum angle of resolution; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

For the population of patients pretreated with prostaglandin analogue monotherapy available for the benefit assessment, only data on the following outcomes were available for the present benefit assessment: all-cause mortality, SAEs, discontinuation due to AEs, ocular AEs, ocular SAEs, and discontinuation due to ocular AEs. There were no evaluable data for the 4 morbidity outcomes. Patient relevance of the operationalization remains unclear for the outcome "OSD". No analyses for the available population were available for the outcomes on visual acuity and visual field defects. Health-related quality of life was not investigated in Study 201051 (see Section 2.7.2.4.3 of the full dossier assessment for a detailed description).

The available data were only based on patients with previous prostaglandin analogue monotherapy (see Section 2.7.2.4.1 of the full dossier assessment).

2.4.2 Risk of bias

Table 9 shows the risk of bias for these outcomes.

Table 9: Risk of bias at study and outcome level – RCT, direct comparison: tafluprost/timolol vs. tafluprost + timolol

Study	Study level	Outcomes										
		All-cause mortality	Ocular surface disease	Improvement of visual acuity[a]	Worsening of visual acuity[a]	Visual field defects	Health-related quality of life	SAEs	Discontinuation due to AEs	Ocular AEs	Ocular SAEs	Discontinuation due to ocular AEs
201051	H	H[b]	-[c]	-[c]	-[c]	-[c]	-[d]	H[b]	H[b]	H[b]	H[b]	H[b]

a: By ≥ 0.2 units on the logMAR scale; equivalent to 10 letters on the ETDRS chart [4].
b: The risk of bias at study level and for all patient-relevant outcomes for which evaluable data are available was rated as high because of the possible violation of the ITT principle.
c: No evaluable data available. For reasons, see Section 2.7.2.4.3 of the full dossier assessment.
d: Outcome was not investigated in the study.
AE: adverse event; ETDRS: Early Treatment Diabetic Retinopathy Study; H: high; ITT: intention to treat; logMAR: logarithm of the minimum angle of resolution; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias was rated as high for all patient-relevant outcomes for which evaluable data were presented in the dossier. The possible violation of the ITT principle was decisive for the assessment. It cannot be excluded that the ITT principle for the available population of patients pretreated with prostaglandin analogue monotherapy was violated because it remains unclear how large the proportion of data is that were not considered in the analysis. No subgroup analysis was conducted for a total of 58 of the 400 (14.5%) randomized patients in the study after previous treatment with IOP-lowering medication, from which the population available for the benefit assessment resulted. There was no information about how these 58 patients were distributed among the corresponding subgroups or how many of these patients would have to be categorized as the subgroup “prostaglandin analogue monotherapy”. It therefore remains unclear how large the actual proportion of patients is for the available population (see also Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment).

The risk of bias was not estimated for the outcomes on OSD, visual acuity and visual field defects and on health-related quality of life because no (evaluable) data were available.

The assessment of the risk of bias in the present benefit assessment deviates from the company’s assessment, which assessed the risk of bias as low for the outcomes included by the company, except for OSD. The company assessed the risk of bias for the outcome “OSD” as high.

2.4.3 Results

Table 10 summarizes the results on the comparison of tafluprost/timolol (fixed combination) with tafluprost + timolol (non-fixed combination) in patients with open-angle glaucoma or ocular hypertension. The available data were only based on the population available for the benefit assessment (proportion of the relevant subpopulation from Study 201051 with pretreatment with prostaglandin analogue monotherapy). Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 10: Results (dichotomous outcomes) – RCT, direct comparison: tafluprost/timolol vs. tafluprost + timolol

Study **Outcome category** **Outcome**	**Tafluprost/timolol**		**Tafluprost + timolol**		**Tafluprost/timolol vs. tafluprost + timolol**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value[a]**
201051					
Mortality					
All-cause mortality	ND	0 (0)	ND	0 (0)	
Morbidity					
Ocular surface disease	No evaluable data[b]				
Improvement of visual acuity[c]	No evaluable data[d]				
Worsening of visual acuity[c]	No evaluable data[d]				
Visual field defects	No evaluable data[d]				
Health-related quality of life	Outcome not investigated				
Adverse events					
AEs	34	14 (41.2)	35	14 (40.0)	
SAEs	34	2 (5.9)	35	1 (2.9)	2.06 [0.20; 21.67]; 0.569
Discontinuation due to AEs	34	0 (0)	35	0 (0)	
Ocular AEs	34	7 (20.6)	35	10 (28.6)	0.72 [0.31; 1.67]; 0.525
Ocular SAEs	34	0 (0)	35	0 (0)	
Discontinuation due to ocular AEs	34	0 (0)	35	0 (0)	

a: Institute's calculation, unconditional exact test (CSZ method according to [5]).
b: Unsuitable operationalization (see Section 2.7.2.4.3 of the full dossier assessment).
c: By ≥ 0.2 units on the logMAR scale; equivalent to 10 letters on the ETDRS chart [4,1].
d: No analyses available for the available population (patients pretreated with prostaglandin analogue monotherapy) (see Section 2.7.2.4.3 of the full dossier assessment).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; ETDRS: Early Treatment Diabetic Retinopathy Study; logMAR: logarithm of the minimum angle of resolution; N: number of analysed patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Mortality

Information on deaths was available for Study 201051. No deaths occurred during the total study duration. There is no hint of an added benefit of tafluprost/timolol in comparison with tafluprost + timolol for this outcome, an added benefit is therefore not proven.

The assessment mentioned above concurs with the assessment of the company, which also derived no added benefit for this outcome.

Morbidity

Ocular surface disease

There were no evaluable data for the outcome "OSD" because there are doubts about the patient relevance of the operationalization presented. There is no hint of an added benefit of tafluprost/timolol in comparison with tafluprost + timolol, an added benefit is therefore not proven.

The assessment mentioned above concurs with the assessment of the company, but the company used the results for the total population of the study for its assessment.

Improvement or worsening of visual acuity, visual field defects

There were no evaluable data for the available population of patients pretreated with prostaglandin analogue monotherapy for the outcomes "improvement or worsening of visual acuity" and "visual field defects". Hence there is no hint of an added benefit of tafluprost/timolol in comparison with tafluprost + timolol for these outcomes, an added benefit is not proven for either of these outcomes.

The company did not use these outcomes in its assessment.

Health-related quality of life

Health-related quality of life was not investigated in the study. There is no hint of an added benefit of tafluprost/timolol in comparison with tafluprost + timolol for this outcome, an added benefit is therefore not proven.

The assessment mentioned above concurs with the company's assessment.

Adverse events

Overall rate of SAEs, discontinuation due to AEs, ocular AEs, ocular SAEs, discontinuation due to ocular AEs

There was no statistically significant difference between the 2 treatment groups for the outcomes "SAEs" and "ocular AEs". There were no discontinuations due to AEs (and hence also no discontinuations due to ocular AEs) or ocular SAEs. There is no hint of greater or lesser harm of tafluprost/timolol versus tafluprost + timolol, greater or lesser harm is therefore not proven for any of the outcomes mentioned above.

The assessment mentioned above concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

No subgroup analyses were available for the available population of patients who were pretreated with prostaglandin analogue monotherapy. The company presented subgroup analyses for the total study population of Study 201051, but these were not relevant for the present benefit assessment (see Sections 2.7.2.2 and 2.7.2.4.3 of the full dossier assessment).

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

Based on the data presented in Section 2.4 there is no proof of added benefit of tafluprost/timolol (fixed combination) in comparison with tafluprost + timolol (non-fixed combination, see Table 11).

Table 11: Extent of added benefit at outcome level: tafluprost/timolol versus tafluprost + timolol

Outcome category **Outcome**	**Tafluprost/timolol vs. tafluprost + timolol** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Ocular surface disease	No evaluable data available	
Improvement of visual acuity[c]	No evaluable data available	
Worsening of visual acuity[c]	No evaluable data available	
Visual field defects	No evaluable data available	
Health-related quality of life		
	Outcome not investigated	
Adverse events		
SAEs	5.9% vs. 2.9% RR 2.06 [0.20; 21.67] p = 0.569	Lesser/greater harm not proven
Discontinuation due to AEs	0% vs. 0%	Lesser/greater harm not proven
Ocular AEs	20.6% vs. 28.6% RR 0.72 [0.31; 1.67] p = 0.525	Lesser/greater harm not proven
Ocular SAEs	0% vs. 0%	Lesser/greater harm not proven
Discontinuation due to ocular AEs	0% vs. 0%	Lesser/greater harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: By ≥ 0.2 units on the logMAR scale; equivalent to 10 letters on the ETDRS chart [4].
AE: adverse event; ETDRS: Early Treatment Diabetic Retinopathy Study; CI: confidence interval; CI_u: upper limit of the CI; logMAR: logarithm of the minimum angle of resolution; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Overall, neither positive nor negative effects remain for tafluprost/timolol for the proportion of the relevant subpopulation available for the benefit assessment (pretreatment with prostaglandin analogue monotherapy).

There was no information on patients pretreated with beta-blocker monotherapy.

In summary, the added benefit of tafluprost/timolol (fixed combination) versus the ACT (tafluprost + timolol in non-fixed combination) is not proven.

The result of the assessment of the added benefit of tafluprost/timolol in comparison with the ACT is summarized in Table 12.

Table 12: Tafluprost/timolol – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Lowering of the IOP 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	Combination therapy of **beta-blocker + prostaglandin analogue** or beta-blocker + prostamide as non-fixed or fixed combination	Added benefit not proven[b]
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: Data were available for patients with previous prostaglandin analogue monotherapy; no data for the benefit assessment were available for patients with previous beta-blocker monotherapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IOP: intraocular pressure		

This deviates from the company's approach, which derived a hint of a non-quantifiable added benefit on the basis of the results for the total study population. It differentiated between the total population and a population designated by the company as "patient population of particular interest", in which it included patients who would develop an acute patient-relevant damage from preservatives, e.g. in case of allergy to preservatives or OSD, or who have the respective risk factors.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

Holló G, Hommer A, Antón Lopez A, Ropo A. Efficacy, safety, and tolerability of preservative-free fixed combination of tafluprost 0.0015%/timolol 0.5% versus concomitant use of the ingredients. J Ocul Pharmacol Ther 2014; 30(6): 468-475.

Santen Oy. Tafluprost-timolol fixed dose combination non-inferiority study against concomitant administrations: full text view [online]. In: ClinicalTrials.gov 7 June 2012 [accessed: 27 February 2015]. URL: https://clinicaltrials.gov/show/NCT01306461.

Santen Oy. A phase III, randomized, double-masked 6-month clinical study to compare the efficacy and safety of the preservative-free fixed dose combination of tafluprost 0.0015% and timolol 0.5% eye drops to those of tafluprost 0.0015% and timolol 0.5% eye drops given concomitantly in patients with open angle glaucoma or ocular hypertension [online]. In: EU Clinical Trials Register. [Accessed: 17 February 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number%3A2010-022984-36.

Santen Oy. A phase III, randomized, double-masked 6-month clinical study to compare the efficacy and safety of the preservative free fixed dose combination of tafluprost 0.0015% and timolol 0.5% eye drops to those of tafluprost 0.0015% and timolol 0.5% eye drops given concomitantly in patients with open angle glaucoma or ocular hypertension: study 201051; clinical study report [unpublished]. 2012.

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 4.1 [online]. 28 November 2013 [accessed: 1 February 2015]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Santen. Taptiqom 15 Mikrogramm/ml + 5 mg/ml Augentropfen im Einzeldosisbehältnis: Fachinformation [online]. December 2014 [accessed: 17 February 2015]. URL: http://www.fachinfo.de.

4. International Society for Low vision Research and Rehabilitation. Guide for the evaluation of visual impairment [online]. 1999 [accessed: 17 February 2015]. URL: http://www.ski.org/Colenbrander/Images/Visual_Impairmnt_Guide.pdf.

5. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Comput Stat Data Anal 1994; 17(5): 555-574.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a14-49-tafluprost/timolol-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6547.html.