IQWiG Reports – Commission No. A21-12

Levofloxacin/dexamethasone (inflammation and infection after cataract surgery) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Levofloxacin/Dexamethason (Entzündungen und Infektionen nach Kataraktoperationen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 April 2021). 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
Levofloxacin/dexamethasone (inflammation and infection after cataract surgery) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
1 February 2021

Internal Commission No.
A21-12

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Daniela Claessens, Ophthalmological Group Practice Lindenthal, 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

- Christina Keksel
- Nadia Abu Rajab
- Katrin Nink
- Sabine Ostlender
- Mattea Patt
- Regine Potthast
- Min Ripoll
- Dorothea Sow

Keywords: Levofloxacin, Dexamethasone, Surgical Wound Infection, Cataract, Benefit Assessment, NCT 03739528

Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ETDRS	Early Treatment Diabetic Retinopathy Study
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)
SPC	Summary of Product Characteristics
TOSS	Total Ocular Symptom Score

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code 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 levofloxacin/dexamethasone. 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 1 February 2021.

Research question

The aim of the present report is the assessment of the added benefit of levofloxacin/dexamethasone in comparison with the appropriate comparator therapy (ACT) for the prevention and treatment of inflammation, and the prevention of infection associated with cataract surgery in adult patients.

For the present benefit assessment, the G-BA's specification of the ACT resulted in the research question presented in Table 2.

Table 2: Research questions of the benefit assessment of levofloxacin/dexamethasone

Therapeutic indication[a]	**ACT**[b]
Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults	Combination of local antibiotic therapy (cefuroxime, polymyxin B/neomycin/gramicidin, **tobramycin**[c], gentamicin, neomycin[c]) **in conjunction with** antiphlogistic mono- or combination therapy: corticosteroid, e.g. rimexolone, **dexamethasone**, fluorometholone, prednisolone, loteprednol etabonate and/or NSAID, e.g. diclofenac, nepafenac, indomethacin, ketorolac
a. In accordance with the G-BA, it is assumed that preoperative antiseptic treatment (e.g. with povidone-iodine) is carried out in the course of cataract surgery and that antibiotic therapy is indicated in the present therapeutic indication. Postoperative antibiotic therapy to prevent infection in the course of cataract surgery is not generally indicated. b. Presentation of the respective 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**. c. Only in fixed combination with dexamethasone. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NSAID: nonsteroidal anti-inflammatory drug	

The company chose the fixed combination of tobramycin/dexamethasone as comparator therapy from the options presented above and thus 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.

Study pool and study design

The randomized, blinded-assessor LEADER-7 study, which compared levofloxacin/ dexamethasone with tobramycin/dexamethasone fixed combination was included in the benefit assessment.

The study included patients aged 40 years and older after completed senile or presenile cataract surgery without complications. The surgical procedure had to be phacoemulsification in all patients.

A total of 808 patients were randomized immediately after cataract surgery in a 1:1 ratio either to treatment with levofloxacin/dexamethasone for 7 days followed by dexamethasone as monotherapy for another 7 days or to treatment with tobramycin/dexamethasone for 14 days. Randomization was stratified by study centres.

Deviating from the Summary of Product Characteristics (SPC), administration of levofloxacin/dexamethasone was not every 6 hours, but at fixed times every 5 hours (± 30 minutes) with an interruption from hours 23:00 to 8:00. The administration of tobramycin/dexamethasone was carried out with restrictions regarding the adjustment of the dose in the first 24 to 48 hours as well as the reduction of the application frequency according to the SPC.

Primary outcome of the study was the absence of signs of anterior chamber inflammation. Patient-relevant secondary outcomes were all-cause mortality, symptoms and adverse events (AEs).

There are several uncertainties about the study design. For example, the company did not provide any information on whether preoperative antiseptic treatment (e.g. with povidone-iodine) was carried out prior to cataract surgery. Besides, it is questionable whether postoperative antibiotic prophylaxis therapy was indicated for all patients in the study. It is also unclear whether the reassessment of the patient recommended in the SPC took place after completion of 1 week of therapy with levofloxacin/dexamethasone to assess the need for continued administration of corticosteroid eye drops as monotherapy. Overall, this did not lead to the exclusion of the study, but the aspects mentioned were included in the assessment of the certainty of conclusions of the results.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low for the LEADER-7 study.

The outcome-specific risk of bias was considered low for the results of the outcomes “all-cause mortality”, “endophthalmitis” and “serious adverse events (SAEs)”. Due to a lack of blinding of the patients in subjective outcome assessment by the patients themselves, the risk of bias of the results of the following outcomes was rated as high: itching/burning, redness of the

conjunctiva, tearing, ocular pain/discomfort, decreased visual acuity, and discontinuation due to AEs.

On the basis of the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes. The rationale for this is that it is unclear whether postoperative antibiotic therapy was indicated in all patients in the LEADER-7 study. In addition, it is unclear whether the 7-day dexamethasone monotherapy following levofloxacin/dexamethasone administration in the intervention arm was indicated for all patients in the total patient population. Furthermore, there is no information on whether preoperative antiseptic treatment was given to all patients. In addition, the risk of bias of the results of the included outcomes (excluding all-cause mortality, endophthalmitis and SAEs) was rated as high.

Results

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". This resulted in no hint of an added benefit of levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone; an added benefit is therefore not proven.

Morbidity

Endophthalmitis

No endophthalmitis occurred during the study. There was no hint of an added benefit of levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone; an added benefit is therefore not proven.

Itching/burning, redness of the conjunctiva, tearing and ocular pain/discomfort (each considered as absence of symptoms)

There were no statistically significant differences between the treatment arms at any documentation time for the following outcomes: itching/burning, redness of the conjunctiva, tearing and ocular pain/discomfort (each considered as absence of symptoms). This resulted in no hint of an added benefit of levofloxacin/dexamethasone in comparison with tobramycin/ dexamethasone; an added benefit is therefore not proven.

Decreased visual acuity

There was no statistically significant difference between the treatment arms for the outcome "decreased visual acuity". This resulted in no hint of an added benefit of levofloxacin/ dexamethasone in comparison with tobramycin/dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

No health-related quality of life outcomes were recorded in the LEADER-7 study.

Side effects

SAEs and discontinuation due to AEs

There were no statistically significant differences between the treatment arms for either of the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone; greater or lesser harm is therefore not proven in either case.

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

On the basis of the results presented, probability and extent of the added benefit of the drug combination of levofloxacin/dexamethasone in comparison with the ACT are assessed as follows:

In summary, there is no hint of an added benefit of levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone for the prevention and treatment of inflammation, and the prevention of infection associated with cataract surgery for adult patients.

Table 3 shows a summary of probability and extent of the added benefit of levofloxacin/ dexamethasone.

[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: Levofloxacin/dexamethasone – probability and extent of added benefit

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults	Combination of local antibiotic therapy (cefuroxime, polymyxin B/neomycin/gramicidin, **tobramycin**[c], gentamicin, neomycin[c]) **in conjunction with** antiphlogistic mono- or combination therapy: corticosteroid, e.g. rimexolone, **dexamethasone**, fluorometholone, prednisolone, loteprednol etabonate and/or NSAID, e.g. diclofenac, nepafenac, indomethacin, ketorolac	Added benefit not proven[d]

a. In accordance with the G-BA, it is assumed that preoperative antiseptic treatment (e.g. with povidone-iodine) is carried out in the course of cataract surgery and that antibiotic therapy is indicated in the present therapeutic indication. Postoperative antibiotic therapy to prevent infection in the course of cataract surgery is not generally indicated.
b. Presentation of the respective 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**.
c. Only in fixed combination with dexamethasone.
d. The LEADER-7 study only included patients aged 40 years and older after cataract surgery by means of phacoemulsification without complications. Therefore, no conclusions can be drawn from the study regarding patients aged < 40 years or with complications during cataract surgery.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NSAID: nonsteroidal anti-inflammatory drug

The approach for the derivation of an overall conclusion on the 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 is the assessment of the added benefit of levofloxacin/ dexamethasone in comparison with the ACT for the prevention and treatment of inflammation, and the prevention of infection associated with cataract surgery in adult patients.

For the present benefit assessment, the G-BA's specification of the ACT resulted in the research question presented in Table 4.

Table 4: Research questions of the benefit assessment of levofloxacin/dexamethasone

Therapeutic indication[a]	**ACT**[b]
Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults	Combination of local antibiotic therapy (cefuroxime, polymyxin B/neomycin/gramicidin, **tobramycin**[c], gentamicin, neomycin[c]) **in conjunction with** antiphlogistic mono- or combination therapy: corticosteroid, e.g. rimexolone, **dexamethasone**, fluorometholone, prednisolone, loteprednol etabonate and/or NSAID, e.g. diclofenac, nepafenac, indomethacin, ketorolac

a. In accordance with the G-BA, it is assumed that preoperative antiseptic treatment (e.g. with povidone-iodine) is carried out in the course of cataract surgery and that antibiotic therapy is indicated in the present therapeutic indication. Postoperative antibiotic therapy to prevent infection in the course of cataract surgery is not generally indicated.
b. Presentation of the respective 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**.
c. Only in fixed combination with dexamethasone.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NSAID: nonsteroidal anti-inflammatory drug

The company chose the fixed combination of tobramycin/dexamethasone as comparator therapy from the options presented above and thus 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.

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 levofloxacin/dexamethasone (status: 9 November 2020)
- bibliographical literature search on levofloxacin/dexamethasone (last search on 9 November 2020)
- search in trial registries/trial results databases for studies on levofloxacin/dexamethasone (last search on 9 November 2020)

- search on the G-BA website for levofloxacin/dexamethasone (last search on 9 November 2020)

To check the completeness of the study pool:

- search in trial registries for studies on levofloxacin/dexamethasone (last search on 16 February 2021)

The check did not identify any additional relevant studies.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: levofloxacin/dexamethasone vs. tobramycin/dexamethasone

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication yes/no [citation])
LEADER-7	Yes	Yes	No	No[c]	Yes [3,4]	Yes [5]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; RCT: randomized controlled trial

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: levofloxacin/dexamethasone vs. tobramycin/dexamethasone

Study	Study design	Population	Interventions (number of patients treated[a])	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
LEADER-7	RCT, open-label[c], parallel	Patients ≥ 40 years of age after completed senile or presenile cataract surgery without complications	Levofloxacin/dexamethasone followed by dexamethasone (N = 395) tobramycin/dexamethasone (N = 393)	Screening: ≤ 28 days Treatment: 14 days[d] Follow-up observation: 7 days for AEs, 30 days for SAEs	51 centres[e] in Germany, Italy, Russia, Spain 9/2018–12/2018	Primary: absence of signs of anterior chamber inflammation Secondary: symptoms, AEs

a. Out of 808 randomized patients, only 788 were treated. Of the 20 patients who were not treated, the withdrawal of consent to participate in the study was the predominant reason for not receiving treatment (14 [70%] patients).
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
c. The outcome assessors were blinded in the study.
d. From the day of surgery immediately after randomization for patients who were not bandaged, or immediately after removal of dressing of the eye.
e. According to the data in the publication on the LEADER-7 study [5], these were 53 centres.

AE: adverse event; N: number of patients included; RCT: randomized controlled trial; SAE: serious adverse event

Table 7: Characteristics of the intervention – RCT, direct comparison: levofloxacin/dexamethasone vs. tobramycin/dexamethasone

Study	Intervention	Comparison
LEADER-7	Levofloxacin 5 mg/mL/dexamethasone 1 mg/mL for 7 days followed by dexamethasone 1 mg/mL for another 7 days	Tobramycin 3 mg/mL/dexamethasone 1 mg/mL for 14 days
	in each case as eye drops, 1 drop – 4 times a day[a]	
	Non-permitted pretreatment ▪ prostaglandin analogues ▪ intravitreal VEGF inhibitors ▪ surgery in the eye to be operated (including laser surgery) ≤ 3 months before study start **Non-permitted concomitant treatment** ▪ topical antibiotics ▪ systemic antibiotics for prophylaxis ▪ topical or systemic corticosteroids	
a. Hours 8:00, 13:00, 18:00 and 23:00, each ± 30 minutes. RCT: randomised controlled trial; VEGF: vascular endothelial growth factor		

Study design

Study LEADER-7 is a randomized, blinded-assessor study comparing levofloxacin/ dexamethasone with tobramycin/dexamethasone fixed combination.

The study included patients aged 40 years and older after completed senile or presenile cataract surgery without complications. The surgical procedure had to be phacoemulsification in all patients. Patients with eye disorders (e.g. blepharitis, conjunctivitis or diabetic retinopathy) and systemic disorders (e.g. rheumatoid arthritis, systemic lupus erythematosus or scleroderma with major ocular involvement) were excluded.

According to various guidelines [6,7], preoperative antiseptic treatment (e.g. with povidone-iodine) should be standard of care for cataract surgery. It is not clear from the information in Module 4 A and the study protocol to what extent such treatment prior to cataract surgery took place in the LEADER-7 study.

A total of 808 patients were randomized immediately after cataract surgery in a 1:1 ratio either to treatment with levofloxacin/dexamethasone for 7 days followed by dexamethasone as monotherapy for another 7 days or to treatment with tobramycin/dexamethasone for 14 days. Randomization was stratified by study centres.

20 of the 808 (approx. 2.5%) patients did not receive treatment with the study medication after randomization. The main reason for this was that patients withdrew their consent to participate in the study (6 out of 8 [75%] patients in the intervention arm and 8 out of 12 [67%] patients in the control arm).

In the LEADER-7 study, administration of levofloxacin/dexamethasone and of tobramycin/ dexamethasone was at fixed times every 5 hours (± 30 minutes) with an interruption from hours 23:00 to 8:00. For levofloxacin/dexamethasone, this deviates from the SPC [8] in that the fixed combination should be administered every 6 hours. For tobramycin/dexamethasone, it is possible according to the SPC [9], to increase the dose to 1 drop every 2 hours during the waking phases in the first 24 to 48 hours and to decrease the frequency of administration based on the improvement in clinical signs. The extent to which this was allowed in the LEADER-7 study is not clear from the study protocol. Overall, however, the deviations described are not considered to be so serious as to have any consequences for the present benefit assessment.

Primary outcome of the study was the absence of signs of anterior chamber inflammation. Patient-relevant secondary outcomes were symptoms and AEs.

Notes on the study design

Unclear need for postoperative antibiotic prophylaxis in all patients

In the LEADER-7 study, all patients received topical antibiotic therapy after completed cataract surgery without complications. It is questionable whether postoperative antibiotic prophylaxis therapy was indicated for all patients in the study, especially since about 80% of the patients received an intracameral antibiotic during surgery.

The company noted that little current evidence is available on postoperative antibiotic prophylaxis. In the company's view, however, it can be inferred from recognized recommendations and guidelines that patients at particular risk of infection require postoperative antibiotic prophylaxis, although a precise quantification of this patient population is not possible.

For the patient population of the LEADER-7 study, the need for postoperative antibiotic prophylaxis resulted from the patients' high age (43% were at least 75 years old), male sex (approx. 40%) and concomitant diseases diabetes mellitus (approx. 17%) and hypertension (approx. 57%).

Overall, the inclusion criteria of the LEADER-7 study were not designed to investigate patients with an increased risk of endophthalmitis, for example, especially as patients with complications of cataract surgery were excluded.

According to guidelines, postoperative prophylactic antibiotic therapy may be an option to reduce infections, especially when risk factors for endophthalmitis are present (e.g. intraoperative rupture of the posterior capsule, vitreous loss, lacrimal duct obstruction, active blepharitis, immunodeficiency, age, and male sex) [6,7,10,11]. However, concrete criteria for deciding for or against the use of topical antibiotics are not explicitly mentioned in the guidelines. Rather, there is a critical discussion about the significance of postoperative topical antibiotics, for example in addition to intracameral antibiotic administration already carried out during surgery. The guidelines also point out the increasing risk of antibiotic resistance [6].

In summary, it is unclear whether postoperative antibiotic prophylaxis therapy was indicated for all patients in the LEADER-7 study. However, no clear criteria for or against prophylactic administration can be derived from the available guidelines. Therefore, the suitability of the LEADER-7 study is not fundamentally questioned. However, the certainty of conclusions of the LEADER-7 study is already limited for this reason alone (see Section 2.4.3).

Subsequent therapy with levofloxacin/dexamethasone in the intervention arm of the study

The SPC [8] recommends reassessment of the patient after completion of 1 week of therapy with levofloxacin/dexamethasone to assess the need for continued administration of corticosteroid eye drops as monotherapy. The duration of treatment may depend on the patient's risk factors and the outcome of the operation and must be determined by the physician after examination with a slit lamp microscope and depending on the severity of the clinical picture.

It is not clear from the information in Module 4 A and the study protocol that such a reassessment of the patients took place in the LEADER-7 study. Rather, all patients in the intervention arm received dexamethasone as monotherapy for another 7 days. This potential deviation from the SPC did not lead to the exclusion of the study, but was included in the assessment of the reliability of the certainty of conclusions of the results (see Section 2.4.3).

Table 8 shows the characteristics of the patients in the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: levofloxacin/dexamethasone vs. tobramycin/dexamethasone (multipage table)

Study Characteristic Category	Levofloxacin/ dexamethasone N[a] = 395	Tobramycin/ dexamethasone N[a] = 393
LEADER-7		
Age [years], mean (SD)	72 (9)	72 (9)
Sex [F/M], %	58/42	61/39
Family origin, n (%)		
Caucasian	393 (99.5)	391 (99.5)
Asian	1 (0.3)	1 (0.3)
Native Americans or Native Alaskans	1 (0.3)	0 (0)
Hawaiian or other Pacific Islanders	0 (0)	1 (0.3)
Concomitant diseases total, n (%)	338 (85.6)	321 (81.7)
Hypertension	224 (56.7)	226 (57.5)
Diabetes mellitus	67 (17.0)	68 (17.3)
Hypercholesterolaemia	56 (14.2)	64 (16.3)
Cardiac disorders	47 (11.9)	66 (16.8)
Osteoporosis	26 (6.6)	22 (5.6)
Hypothyroidism	35 (8.9)	28 (7.1)
Signs of anterior chamber inflammation[b], n (%)		
Anterior chamber cells	0 (0)	0 (0)
Flare (Tyndall effect)	0 (0)	0 (0)
Conjunctival hyperaemia[b], n (%)		
Mild	13 (3.3)	14 (3.6)
Moderate	0 (0)	1 (0.3)
Intraocular pressure[b] [mmHg], median (min; max)		
Eye to be operated	15 (8; 23)	15 (10; 23)
Eye not to be operated	15 (8; 23)	15 (10; 23)
Visual acuity[b, c] [decimal], median (min; max)		
Eye to be operated	0.40 (0.00; 2.00)	0.40 (0.00; 3.03)
Eye not to be operated	0.80 (0.25; 2.00)	0.70 (0.25; 2.00)
Type of surgery, n (%)		
Phacoemulsification	395 (100)	393 (100)
Intracameral antibiotic, n (%)		
Yes	316 (80.0)	315 (80.2)
No	79 (20.0)	78 (19.9)
Surgical time [minutes], median (min; max)	15 (5; 53)	15 (5; 52)
Treatment discontinuation, n (%)	7 (1.8[d])	5 (1.3[d])
Study discontinuation, n (%)	6 (1.5)[d]	2 (0.5)[d]

Table 8: Characteristics of the study population – RCT, direct comparison: levofloxacin/dexamethasone vs. tobramycin/dexamethasone (multipage table)

Study Characteristic Category	Levofloxacin/ dexamethasone N[a] = 395	Tobramycin/ dexamethasone N[a] = 393
a. Number of treated patients. b. Recorded at screening before cataract surgery. c. Quotient of the distance to the vision test chart and the size of the smallest line readable by the patient; a value of 1.0 corresponds to a visual acuity of 100%. d. Institute's calculation. F: female; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of treated patients; RCT: randomized controlled trial; SD: standard deviation		

The characteristics of the study population are largely comparable between both treatment arms. The mean age of the patients was 72 years, and about 60% were female. Phacoemulsification was the surgical procedure in all patients, and about 80% of the patients received an intracameral antibiotic.

In accordance with the inclusion criterion, all patients in the study had cataract surgery without complications. In addition, only patients ≥ 40 years of age were included in the study. Therefore, on the basis of this study, no conclusions can be drawn on the added benefit for patients < 40 years of age or with complications during the course of surgery.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: levofloxacin/dexamethasone vs. tobramycin/dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
LEADER-7	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the LEADER-7 study. This concurs with the company's assessment.

Limitations resulting from the lack of blinding of the patients and the treating staff are described in Section 2.4 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that all cataract operations were performed using phacoemulsification, which is a widespread surgical procedure in Germany. The company stated that, at the same time, the postoperative topical subsequent treatment with antibiotics and corticosteroids in the form of eye drops carried out in the study represents the German health care standard for the prevention and treatment of inflammation and for the prophylaxis of infections after cataract surgery. In the opinion of the company, the results of the LEADER-7 study can be fully transferred to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - endophthalmitis
  - itching/burning, assessed as a single item of the Total Ocular Symptom Score (TOSS)
  - redness of the conjunctiva, recorded as a single item of the TOSS
  - tearing, recorded as a single item of the TOSS
  - ocular pain/discomfort, recorded using the ocular pain/discomfort score
  - decreased visual acuity recorded with the Snellen or Early Treatment Diabetic Retinopathy Study (ETDRS) chart according to local clinical practice
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: levofloxacin/dexamethasone vs. tobramycin/dexamethasone

Study	Outcomes										
	All-cause mortality	Endophthalmitis	Itching/burning[a]	Redness of the conjunctiva[a]	Tearing[a]	Ocular pain/discomfort	Decreased visual acuity[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Specific AEs
LEADER-7	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	No[d]

a. Recorded as a single item of the TOSS.
b. Presented in the outcome category of side effects in the company's dossier.
c. Outcome not recorded.
d. No specific AEs were identified.

AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; TOSS: Total Ocular Symptom Score

Patient-reported outcomes

Itching/burning, redness of the conjunctiva and tearing

In the LEADER-7 study, patient-reported ocular symptoms were recorded using the TOSS instrument. The TOSS includes patient-reported assessment of 3 ocular symptoms: itching/burning, redness of the conjunctiva and tearing. The occurrence and severity of each symptom was assessed by the patient on days 4, 8 and 15 of the study, with a score from 0 to 3 points (0 = absent, 1 = mild, 2 = moderate, 3 = severe). The question that is asked to the patients for the recording of their symptoms does not include which period of time the patients should look at when answering the question. Due to the frequent recording in each case at intervals of a few days, it is not assumed that this had a relevant influence on the results in the present case.

For the derivation of the added benefit, the company used the analysis of the proportion of patients with a total TOSS score of 0 (i.e. absence of all 3 symptoms). The company did not provide any sources from which the development and validity of the TOSS can be inferred. However, the individual symptoms recorded are patient-relevant and face valid.

In addition to the analyses of the total score, the company also presented analyses of the proportion of patients with symptoms for each of the 3 individual ocular symptoms in Module 4 A. In deviation from the procedure of the company, the present benefit assessment uses these analyses for the derivation of the added benefit.

Ocular pain/discomfort

The ocular pain/discomfort score is a patient-reported assessment of ocular pain and discomfort. The patient assessed the severity of the symptoms on days 4, 8 and 15 of the study, with a score from 0 to 3 points (0 = absent, 1 = mild, 2 = moderate, 3 = severe).

The company did not specify which specific question the patients were asked and which time period the patients were to consider when answering the question. Regardless of this, the outcome was assessed as patient-relevant and, based on the available information, as sufficiently interpretable in the present situation. The outcome was therefore used in the present benefit assessment.

Side effects

In the LEADER-7 study, local tolerability was also assessed by the patients themselves using a 4-point scale. The outcome "local tolerability" assessed general tolerability as well as the 3 individual AEs "burning", "stinging" and "blurred vision".

The AEs mentioned partly overlap with the symptoms already recorded with the TOSS. In addition, no information is available on how the specific recording was carried out with regard to local tolerability, for example by a temporal reference to the application. The outcomes on local tolerability were therefore not used in the present benefit assessment. Regardless of this, statistically significant differences did not occur at any documentation time.

2.4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: levofloxacin/dexamethasone vs. tobramycin/dexamethasone

Study		Outcomes										
	Study level	All-cause mortality	Endophthalmitis	Itching/burning[a]	Redness of the conjunctiva[a]	Tearing[a]	Ocular pain/discomfort	Decreased visual acuity[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Further specific AEs
LEADER-7	L	L	L	H[c]	H[c]	H[c]	H[c]	H[c]	–[d]	L	H[c]	–

a. Recorded as a single item of the TOSS.
b. Presented in the outcome category of side effects in the company's dossier.
c. Lack of blinding (patient) in subjective recording of outcomes.
d. Outcome not recorded.

AE: adverse event; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; TOSS: Total Ocular Symptom Score

The outcome-specific risk of bias for the results of the outcomes "all-cause mortality" and "endophthalmitis" was regarded as low. This concurs with the company's assessment. The risk of bias was also rated as low for the results of the outcome "SAEs". This deviates from the assessment of the company, which rated the risk of bias across outcomes for the results of all AE outcomes as high due to the lack of blinding of the patients.

Due to a lack of blinding of the patients in subjective outcome assessment, the risk of bias of the results of the following outcomes was rated as high: itching/burning, redness of the conjunctiva, tearing, ocular pain/discomfort, decreased visual acuity, and discontinuation due to AEs. This concurs with the company's assessment.

2.4.3 Results

Table 12 summarizes the results for the comparison of levofloxacin/dexamethasone against tobramycin/dexamethasone for the prevention and treatment of inflammation, and the prevention of infection associated with cataract surgery in adult patients. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The results on common AEs, SAEs and discontinuations due to AEs are presented in Appendix A of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: levofloxacin/dexamethasone vs. tobramycin/dexamethasone (multipage table)

Study Outcome category Outcome Time point	Levofloxacin/ dexamethasone		Tobramycin/ dexamethasone		Levofloxacin/ dexamethasone vs. tobramycin/dexamethasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
LEADER-7					
Mortality					
All-cause mortality	395	1 (0.3)	393	0 (0)	2.98 [0.12; 73.05]; 0.516
Morbidity					
Endophthalmitis	395	0 (0)	393	0 (0)	–
Itching/burning (absence of symptoms)[b]					
Day 4	393	350 (89.1)	393	339 (86.3)	1.03 [0.98; 1.09]; 0.248
Day 8	391	350 (89.5)	393	339 (86.3)	1.04 [0.99; 1.09]; 0.212
Day 15	389	360 (92.5)	391	360 (92.1)	1.01 [0.97; 1.05]; 0.869
Redness of the conjunctiva (absence of symptoms)[b]					
Day 4	393	359 (91.3)	393	344 (87.5)	1.04 [0.99; 1.10]; 0.084
Day 8	391	364 (93.1)	393	374 (95.2)	0.98 [0.94; 1.01]; 0.248
Day 15	389	372 (95.6)	391	373 (95.4)	1.00 [0.97; 1.03]; 0.919
Tearing (absence of symptoms)[b]					
Day 4	393	360 (91.6)	393	363 (92.4)	0.99 [0.95; 1.03]; 0.753
Day 8	391	366 (93.6)	393	371 (94.4)	0.99 [0.96; 1.03]; 0.683
Day 15	389	373 (95.9)	391	381 (97.4)	0.98 [0.96; 1.01]; 0.248
Ocular pain/discomfort (absence of symptoms)[c]					
Day 4	395	360 (91.1)	393	361 (91.9)	0.99 [0.95; 1.04]; 0.794
Day 8	395	366 (92.7)	393	366 (93.1)	0.99 [0.96; 1.03]; 0.859
Day 15	395	377 (95.4)	393	373 (94.9)	1.01 [0.97; 1.04]; 0.794
Decreased visual acuity[d]	389	5 (1.3)	391	11 (2.8)	0.46 [0.16; 1.30]; 0.144
Side effects					
AEs (supplementary information)	395	56 (14.2)	393	51 (13.0)	–
SAEs	395	4 (1.0)	393	2 (0.5)	1.99 [0.37; 10.8]; 0.533
Discontinuation due to AEs	395	4 (1.0)	393	3 (0.8)	1.33 [0.30; 5.89]; 0.794

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [12]). In case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
b. Recording as a single item of the TOSS; without imputation of missing values
c. With imputation of missing values using the LOCF method.
d. Visual acuity did not change in 9 (2.3%) patients in the intervention arm and in 8 (2.1%) patients in the comparator arm.

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: levofloxacin/dexamethasone vs. tobramycin/dexamethasone (multipage table)

Study Outcome category Outcome Time point	Levofloxacin/ dexamethasone		Tobramycin/ dexamethasone		Levofloxacin/ dexamethasone vs. tobramycin/dexamethasone
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
AE: adverse event; CI: confidence interval; LOCF: last observation carried forward; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TOSS: Total Ocular Symptom Score					

On the basis of the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes. The rationale for this is that it is unclear whether postoperative antibiotic therapy was indicated in all patients in the LEADER-7 study (see Section 2.3.2). In addition, it is unclear whether the 7-day dexamethasone monotherapy following levofloxacin/dexamethasone administration in the intervention arm was indicated for all patients in the total patient population. Furthermore, there is no information on whether preoperative antiseptic treatment was given to all patients. In addition, the risk of bias of the results of the included outcomes (excluding all-cause mortality, endophthalmitis and SAEs) was rated as high.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". This resulted in no hint of an added benefit of levofloxacin/ dexamethasone in comparison with tobramycin/dexamethasone; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Endophthalmitis

Operationalization

The outcome "endophthalmitis" was recorded on days 4, 8 and 15 of the study. The diagnosis of endophthalmitis was based on clinical assessment of signs such as swollen eyelids, ocular pain, conjunctival hyperaemia, decreased visual acuity, and an opaque vitreous by slit lamp examination and microbiological testing of conjunctival or corneal swabs.

Result

No endophthalmitis occurred during the study. There was no hint of an added benefit of levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived a hint of an added benefit. As justification, the company cited a shortening of the antibiotic treatment duration by administration of levofloxacin/dexamethasone and the clinical benefits and reduced risks for the development of antibiotic resistance the company considered to be associated with this.

Itching/burning, redness of the conjunctiva and tearing (each considered as absence of symptoms)

There were no statistically significant differences between the treatment arms at any documentation time for the following outcomes: itching/burning, redness of the conjunctiva, and tearing (each considered as absence of symptoms). This resulted in no hint of an added benefit of levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone; an added benefit is therefore not proven.

This deviates from the assessment of the company insofar as the company did not use these outcomes separately. However, on the basis of the TOSS (Total Ocular Symptom Score of the 3 symptoms), the company also considered an added benefit as not proven.

Ocular pain/discomfort (absence of symptoms)

There was no statistically significant difference between the treatment arms at any documentation time for the outcome "ocular pain/discomfort" (absence of symptoms). This resulted in no hint of an added benefit of levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone; an added benefit is therefore not proven.

This concurs with the company's assessment.

Decreased visual acuity

There was no statistically significant difference between the treatment arms for the outcome "decreased visual acuity". This resulted in no hint of an added benefit of levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

No health-related quality of life outcomes were recorded in the LEADER-7 study.

Side effects

SAEs and discontinuation due to AEs

There were no statistically significant differences between the treatment arms for either of the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone; greater or lesser harm is therefore not proven in either case.

This concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present benefit assessment:

- age (< 75 years, ≥ 75 years)
- sex (female, male)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

No subgroup analyses are available for the individual symptoms of itching/burning, redness of the conjunctiva and tearing (each considered as absence of symptoms). In accordance with the methods described, no relevant effect modification by age or sex was identified for the remaining outcomes.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, 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 the 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 the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 13).

Table 13: Extent of added benefit at outcome level: levofloxacin/dexamethasone vs. tobramycin/dexamethasone (multipage table)

Outcome category **Outcome** **Time point**	**Levofloxacin/ dexamethasone vs. tobramycin/dexamethasone** **Proportion of events (%)** **RR [95% CI];** **p-value**	**Derivation of extent[a]**
Mortality		
All-cause mortality	0.3% vs. 0% 2.98 [0.12; 73.05]; p = 0.516	Lesser benefit/added benefit not proven
Morbidity		
Endophthalmitis	0% vs. 0% –	Lesser benefit/added benefit not proven
Itching/burning (absence of symptoms)		
Day 4	89.1% vs. 86.3% 1.03 [0.98; 1.09]; p = 0.248	Lesser benefit/added benefit not proven
Day 8	89.5% vs. 86.3% 1.04 [0.99; 1.09]; p = 0.212	Lesser benefit/added benefit not proven
Day 15	92.5% vs. 92.1% 1.01 [0.97; 1.05]; p = 0.869	Lesser benefit/added benefit not proven
Redness of the conjunctiva (absence of symptoms)		
Day 4	91.3% vs. 87.5% 1.04 [0.99; 1.10]; p = 0.084	Lesser benefit/added benefit not proven
Day 8	93.1% vs. 95.2% 0.98 [0.94; 1.01]; p = 0.248	Lesser benefit/added benefit not proven
Day 15	95.6% vs. 95.4% 1.00 [0.97; 1.03]; p = 0.919	Lesser benefit/added benefit not proven
Tearing (absence of symptoms)		
Day 4	91.6% vs. 92.4% 0.99 [0.95; 1.03]; p = 753	Lesser benefit/added benefit not proven
Day 8	93.6% vs. 94.4% 0.99 [0.96; 1.03]; p = 0.683	Lesser benefit/added benefit not proven
Day 15	95.9% vs. 97.4% 0.98 [0.96; 1.01]; p = 0.248	Lesser benefit/added benefit not proven

Table 13: Extent of added benefit at outcome level: levofloxacin/dexamethasone vs. tobramycin/dexamethasone (multipage table)

Outcome category **Outcome** **Time point**	**Levofloxacin/ dexamethasone vs. tobramycin/dexamethasone** **Proportion of events (%)** **RR [95% CI];** **p-value**	**Derivation of extent[a]**
Ocular pain/discomfort (absence of symptoms)		
Day 4	91.1% vs. 91.9% 0.99 [0.95; 1.04]; p = 0.794	Lesser benefit/added benefit not proven
Day 8	92.7% vs. 93.1% 0.99 [0.96; 1.03]; p = 0.859	Lesser benefit/added benefit not proven
Day 15	95.4% vs. 94.9% 1.01 [0.97; 1.04]; p = 0.794	Lesser benefit/added benefit not proven
Decreased visual acuity	1.3% vs. 2.8% 0.46 [0.16; 1.30]; p = 0.144	Lesser benefit/added benefit not proven
Health-related quality of life		
–	Outcomes from this category were not recorded	Lesser benefit/added benefit not proven
Side effects		
SAEs	1.0% vs. 0.5% 1.99 [0.37; 10.8]; p = 0.533	Greater/lesser harm not proven
Discontinuation due to AEs	1.0% vs. 0.8% 1.33 [0.30; 5.89]; p = 0.794	Greater/lesser harm not proven

a. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).

AE: adverse event; CI: confidence interval; RR: relative risk; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

Table 14 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone

Positive effects	**Negative effects**
–	–

In summary, there is no hint of an added benefit of levofloxacin/dexamethasone in comparison with tobramycin/dexamethasone for the prevention and treatment of inflammation, and the prevention of infection associated with cataract surgery for adult patients.

The assessment described above deviates from that of the company, which overall derived a hint of a non-quantifiable added benefit for levofloxacin/dexamethasone. The company justified this with the reduction in conjunctival hyperaemia at the first of the 3 documentation times in patients with concomitant diabetes mellitus. Instead of this outcome assessed by investigators, the present benefit assessment considered the outcome "redness of the conjunctiva", which was recorded as a single item of the TOSS and is based on a self-assessment by the patients.

As a further justification for the derivation of a non-quantifiable added benefit, the company referred in particular to the consideration of the resistance situation in addition to a shortening of the antibiotic and the overall treatment duration. For this purpose, the company mainly used in vitro data on the development of resistance, but did not systematically analyse them.

In its conclusion on the added benefit, the company referred to the dynamic resistance situation in ophthalmology, which, from the company's point of view, requires a sufficient selection of antibiotics. Due to the broad efficacy profile, the company attached particular importance to levofloxacin. However, these conclusions are not relevant to the research question of the early benefit assessment, but to that of the approval. Finally, it is also to be expected that relevant differences in resistance are also reflected in the occurrence of ocular infections.

Table 15 summarizes the result of the assessment of the added benefit of levofloxacin/ dexamethasone in comparison with the ACT.

Table 15: Levofloxacin/dexamethasone – probability and extent of added benefit

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults	Combination of local antibiotic therapy (cefuroxime, polymyxin B/neomycin/gramicidin, **tobramycin**[c], gentamicin, neomycin[c]) **in conjunction with** antiphlogistic mono- or combination therapy: corticosteroid, e.g. rimexolone, **dexamethasone**, fluorometholone, prednisolone, loteprednol etabonate and/or NSAID, e.g. diclofenac, nepafenac, indomethacin, ketorolac	Added benefit not proven[d]

a. In accordance with the G-BA, it is assumed that preoperative antiseptic treatment (e.g. with povidone-iodine) is carried out in the course of cataract surgery and that antibiotic therapy is indicated in the present therapeutic indication. Postoperative antibiotic therapy to prevent infection in the course of cataract surgery is not generally indicated.
b. Presentation of the respective 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**.
c. Only in fixed combination with dexamethasone.
d. The LEADER-7 study only included patients aged 40 years and older after cataract surgery by means of phacoemulsification without complications. Therefore, no conclusions can be drawn from the study regarding patients aged < 40 years or with complications during cataract surgery.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NSAID: nonsteroidal anti-inflammatory drug

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. 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.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 30.12.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. NTC. An international, multicenter, randomized, blinded-assessor, parallel-group clinical study comparing eye drops of combined LEvofloxAcin + DExamethasone foR 7 days followed by dexamethasone alone for an additional 7 days vs. tobramycin + dexamethasone for 14 days for the prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults – LEADER 7 [online]. [Accessed: 12.04.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-000286-36.

4. NTC. Levo-Dexa vs. Tobra+Dexa for Prevention and Treatment of Inflammation and Prevention of Infection in Cataract Surgery (LEADER7) [online]. 2020. URL: https://ClinicalTrials.gov/show/NCT03739528.

5. Bandello F, Coassin M, Di Zazzo A et al. One week of levofloxacin plus dexamethasone eye drops for cataract surgery: an innovative and rational therapeutic strategy. Eye (Lond) 2020; 34(11): 2112-2122. https://dx.doi.org/10.1038/s41433-020-0869-1.

6. American Academy of Ophthalmology. Cataract in the Adult Eye Preferred Practice Pattern [online]. 2016. URL: https://www.aao.org/preferred-practice-pattern/cataract-in-adult-eye-ppp-2016.

7. Barry P, Cordovés L, Gardner S. ESCRS Guidelines for Prevention and Treatment of Endophthalmitis Following Cataract Surgery: Data, Dilemmas and Conclusions [online]. 2013. URL: https://www.escrs.org/downloads/Endophthalmitis-Guidelines.pdf.

8. Santen Oy. Fachinformation Ducressa 1 mg/ml + 5 mg/ml Augentropfen, Lösung. Stand September 2020. 2020.

9. Novartis Pharma. Fachinformation TOBRADEX [online]. 2019. URL: https://www.fachinfo.de.

10. Deutschsprachige Gesellschaft für Intraokularlinsen-Implantation, interventionelle und refraktive Chirurgie. Leitlinie zur Prophylaxe und Therapie von Endophthalmitiden [online]. 2005. URL: http://www.dgii.org/uploads/pdfs/LeitlinieEndophthalmitis_2005.pdf.

11. Canadian Ophthalmological Society. Canadian Ophthalmological Society evidence-based clinical practice guidelines for cataract surgery in the adult eye. Canadian journal of ophthalmology Journal canadien d'ophtalmologie 2008; 43: S7-S33. https://dx.doi.org/10.3129/i08-133.

12. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-12.html.