Resolution

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII - Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V Levofloxacin/ Dexamethasone (Infections and inflammations in connection with cataract surgery)

of 15 July 2021

At its session on 15 July 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient levofloxacin/dexamethasone as follows:

Levofloxacin/dexamethasone

Resolution of: 15 July 2021
Entry into force on: 15 July 2021
BAnz AT TT. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 7 September 2020):

Ducressa eye drops solution is indicated for prevention and treatment of inflammation, and prevention of infection associated with cataract surgery in adults.

Therapeutic indication of the resolution (resolution of 15.07.2021):

see therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Patient population: Prevention and treatment of inflammation, and prevention of infection associated with cataract surgery in adults

Appropriate comparator therapy:

A combination of local antibiotic therapy (cefuroxime, polymyxin B/neomycin/gramicidin, tobramycin[1], gentamicin, neomycin[1]) in conjunction with mono- or combination anti-inflammatory therapy: Corticosteroid, e.g. rimexolone, dexamethasone, fluorometholone, prednisolone, loteprednol etabonate and/or NSAIDs, e.g. diclofenac, nepafenac, indomethacin, ketorolac

Extent and probability of the additional benefit of levofloxacin/dexamethasone compared to tobramycin/dexamethasone:

An additional benefit is not proven

[1]Only in fixed combination with dexamethasone

Study results according to endpoints:[2]

Patient population: Prevention and treatment of inflammation, and prevention of infection associated with cataract surgery in adults

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	↔	No relevant difference for the benefit assessment
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	↔	No relevant difference for the benefit assessment

Explanations:
↑ statistically significant and relevant positive effect with low/unclear reliability of data
↓ statistically significant and relevant negative effect with low/unclear reliability of data
↑↑ statistically significant and relevant positive effect with high reliability of data
↓↓ statistically significant and relevant negative effect with high reliability of data
↔ no statistically significant or relevant difference
∅: there are no usable data for the benefit assessment.
n.a.: not assessable

LEADER-7 study: Levofloxacin/dexamethasone vs tobramycin/dexamethasone

Study design: RCT, open[3], parallel

Mortality

Endpoint	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]
Mortality					

[2] Data from the dossier assessment of the IQWiG (A21-12) and from the addendum (G21-18), unless otherwise indicated.
[3]The endpoint collectors were blinded in the study

Overall mortality	395	1 (0.3)	393	0 (0)	2.98 [0.12; 73.05]; 0.516

Morbidity

Endpoint	**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]
Morbidity					
Endophthalmitis	395	0 (0)	393	0 (0)	–
Itching/burning (symptom-free)[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 (symptom-free)[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
Tear formation (symptom-free)[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 (symptom-free)[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
Visual acuity loss	389	5 (1.3)	391	11 (2.8)	0.46 [0.16; 1.30]; 0.144

Health-related quality of life

No health-related quality of life endpoints were collected in the LEADER 7 study.

Side effects

Endpoint	**Levofloxacin/ dexamethasone**		**Tobramycin/ dexamethasone**		**Levofloxacin/ dexamethasone vs Tobramycin/ dexamethasone**
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value
Side effects					
AE (presented additionally)	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 because of AEs	395	4 (1.0)	393	3 (0.8)	1.33 [0.30; 5.89]; 0.794

a. own calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method). In the case of 0 events in one study arm, the correction factor 0.5 was used in both study arms when calculating effect and CI.
b. determined as a single item of the TOSS; without replacement of missing values
c. with replacement of missing values using LOCF method
d. visual acuity did not change in 9 (2.3%) subjects in the intervention arm and 8 (2.1%) in the comparator arm.

Abbreviations used:
CI = confidence interval; LOCF = last observation carried forward; N = number of subjects evaluated; n = number of subjects with (at least 1) event; N = number of subjects with (at least 1) event; RCT= randomised controlled trial; RR = relative risk; SAE = serious adverse event; TOSS = ocular symptom total score; AE = adverse event; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

Prevention and treatment of inflammation, and prevention of infection associated with cataract surgery in adults

approx. 454,000 to 811,000

Requirements for a quality-assured application

The requirements in the product information are to be taken into account.

3. Treatment costs

Annual treatment costs:

Prevention and treatment of inflammation, and prevention of infection associated with cataract surgery in adults

Designation of the therapy	Costs/patient/operated eye
Medicinal product to be assessed:	
Levofloxacin/dexamethasone	€ 20.02
Appropriate comparator therapy:	
a local antibiotic therapy	
Cefuroxime	No additional costs, as included in the flat rate for outpatient cataract surgery
Combination medicinal product	
Polymyxin B/neomycin/gramicidin	€ 15.57
Tobramycin/dexamethasone	€ 15.38
Gentamicin/dexamethasone (ointment and drops)	€ 11.63 - € 12.56
Neomycin / dexamethasone	€ 13.39
Neomycin/polymyxin B/dexamethasone (drops and ointment)	€ 16.67
in conjunction with anti-inflammatory monotherapy or combination therapy:	
Corticosteroid	
Dexamethasone (drops and ointment)	€ 12.18 - € 15.88
Fluorometholone	€ 12.69
Prednisolone (drops, gel, ointment and cream)	€ 12.84 - € 19.32
Loteprednol	€ 17.01

Designation of the therapy	Costs/patient/operated eye
NSAID	
Diclofenac	€ 15.15
Nepafenac	€ 26.59
Ketorolac	€ 15.56
Flurbiprofen	€ 87.99
local antibiotic therapy + corticosteroid	€ 11.63 - € 34.89[4]
local antibiotic therapy + NSAID	€ 30.72 - € 103.56[5]
local antibiotic therapy + corticosteroid + NSAID	€ 26.78 - € 122.88[6]

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 June 2021)

Costs for additionally required SHI services: not applicable.

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 15 July 2021.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 15 July 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

[4] The range is composed of the lower limit for therapy with gentamicin/dexamethasone and polymyxin B/neomycin/gramicidin in combination with the upper limit for therapy with prednisolone.
[5] The range is composed of polymyxin B/neomycin/gramicidin + diclofenac and polymyxin B/neomycin/gramicidin + flurbiprofen.
[6] The range is composed of the lower limit for therapy with gentamicin/dexamethasone + diclofenac and polymyxin B/neomycin/gramicidin in combination with the upper limit for therapy with prednisolone and flurbiprofen.