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³University of Southern Denmark, Odense, Denmark; ⁴Alcon Inc., Fort Worth, TX, United States**CONFLICT OF INTEREST**

A.V. Margulis, S. Perez-Gutthann, and A. Arana are employees of RTI Health Solutions, which has been compensated for this research. RTI is a nonprofit research institution that conducts work for government, public, and private organizations, including pharmaceutical companies. E. Houben and J. Overbeek are employees of the PHARMO Institute for Drug Outcomes Research (PHARMO). This independent research institute performs financially supported studies for government and related health care authorities and several pharmaceutical companies.

BACKGROUND

- Nevanac (nepafenac) 1 mg/mL and Nevanac 3 mg/mL are available in the European Union for prevention and treatment of postoperative pain and inflammation after cataract surgery, for the first 2 weeks of the postoperative period. Treatment can be extended to the first 3 weeks of the postoperative period, as directed by the clinician.
- In 2011, Nevanac 1 mg/mL was approved for reduction in risk of postoperative macular edema associated with cataract surgery in adult patients with diabetes, for up to 60 days after surgery.
- Other ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) are approved for other uses, creating a potential for off-label use of nepafenac.

OBJECTIVES

- To evaluate the use of nepafenac with regard to the approved indications, focusing on age, cataract surgery, and duration of use in patients with cataract surgery with and without diabetes.
- To provide context to the findings, we explored the use of the ophthalmic NSAIDs ketorolac and diclofenac.

METHODS**Study Design and Data Sources**

- Conducted an observational cohort study of users of nepafenac, ketorolac, and diclofenac from September 2008 through October 2013 in The Netherlands (PHARMO) and October 2008 through December 2014 in Denmark (national databases)

Study Population

- Included patients in the cohort after 6 months of enrollment (with the first prescription for the drug after 6 months free of prescriptions for that drug in Denmark)
- Continued follow-up until the earliest of disenrollment, death, or end of study period

Therapy Episodes

- Created therapy episodes by concatenating dispensed ambulatory prescriptions without treatment gaps
- Derived the indication from diagnoses and procedures dated within 30 days before and 30 days after the prescription dispensing date
- Included multiple episodes by individual patients

Cataract Surgeries

- The Netherlands: identified from procedures in hospital discharge records
- Denmark: identified from diagnostic and procedure codes in hospital discharge records and from the registry that records procedures conducted under specialist care

Sensitivity Analyses

- Conducted the following sensitivity analyses to address underrecording of cataract surgery:
 - Expanded the list of ophthalmic conditions for which nepafenac might be used off-label (The Netherlands and Denmark)
 - Identified the presence of correspondence between general practitioners and ophthalmologists (The Netherlands)
 - Conducted subgroup analyses in patients whose surgeries were likely to be captured better in the Danish data: sicker patients (Charlson Comorbidity Index score ≥ 3) and the elderly (aged ≥ 80 years)¹²

Duration of Therapy

- Used the number of dispensed bottles as a proxy for therapy duration for nepafenac, assuming that one bottle of nepafenac (3 mL or 5 mL) represented treatment ≤ 21 days and two bottles represented treatment ≤ 60 days

Study Registration

- Registered the study and its protocol in the EU PAS register on 27 November 2013, prior to the start of data collection³

RESULTS**Users and Use**

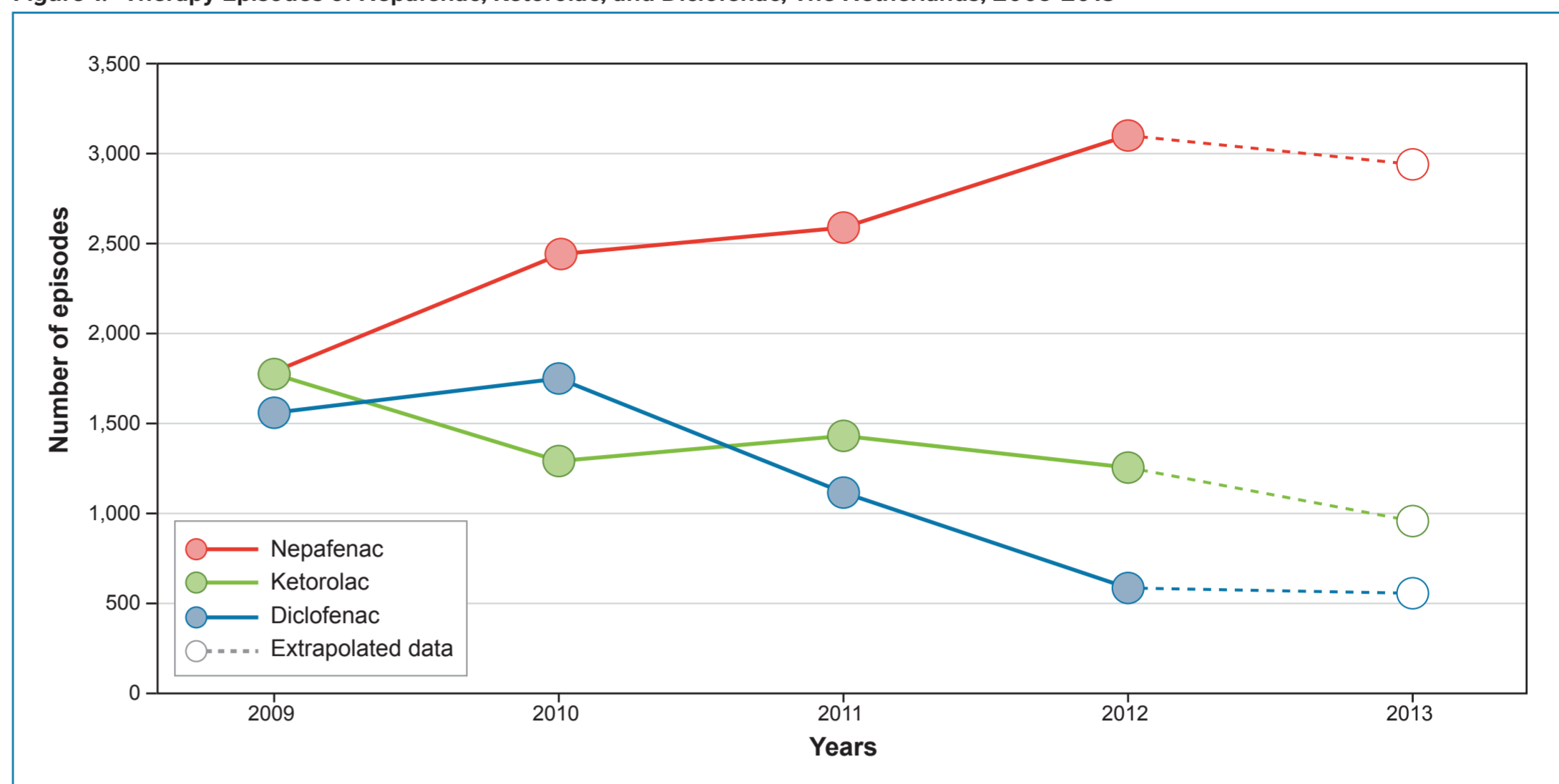
- The Netherlands: 9,530 nepafenac users (12,691 therapy episodes), 5,351 ketorolac users (7,540 therapy episodes), and 4,536 diclofenac users (5,950 therapy episodes) (Tables 1 and 2)
- Denmark: 60,403 users of nepafenac (73,648 therapy episodes), 54,185 users of ketorolac (102,334 therapy episodes), and 131,440 users of diclofenac (184,361 therapy episodes)

Duration of Therapy

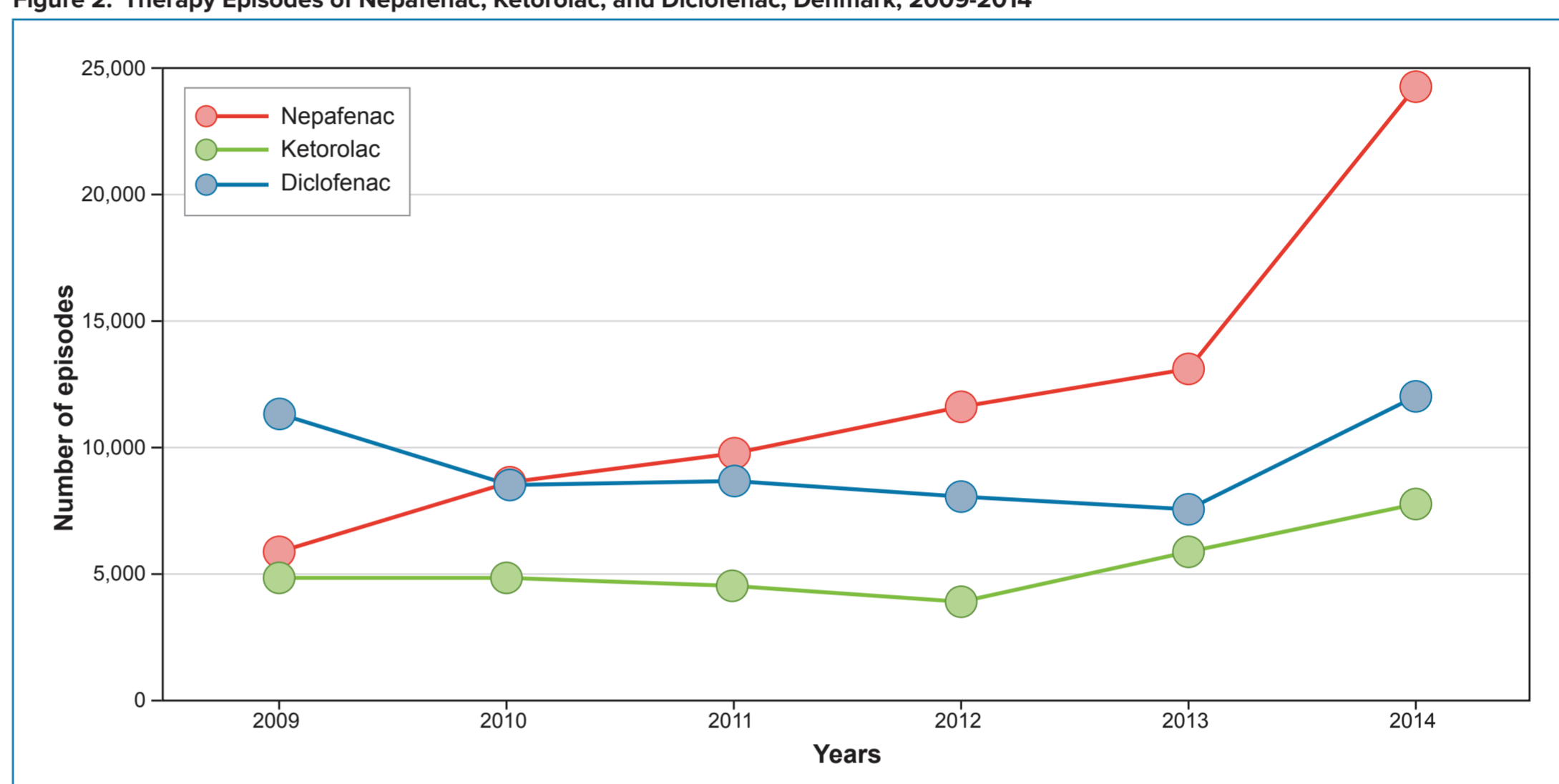
- The Netherlands: 60% of adult patients with recorded cataract surgery and no diabetes used one bottle per episode (within the label limits), and 90% of adult patients with recorded cataract surgery and diabetes used up to two bottles (within the label limits).
- Denmark: 92% of adult patients with recorded cataract surgery and no diabetes used one bottle per episode (within the label limits), and 99.8% of adult patients with recorded cataract surgery and diabetes used up to two bottles (within the label limits).

DISCUSSION

- The main limitation of this study is the incomplete capture of cataract surgeries and other ophthalmic procedures and conditions.
 - The Netherlands: The data source captures admissions > 24 hours and admissions < 24 hours for which a bed is required.
 - Denmark: Cataract surgeries are recorded in the Danish National Patient Registry. In 2002, to shorten the wait for this surgery, cataract surgeries started being offered by private hospitals or clinics at government expense.¹ Although mandatory, reporting of these surgeries was found to be incomplete.¹²
 - We used number of bottles prescribed as the best proxy for duration of use. To assume that the full bottle was used in each episode would result in overestimation of duration.
 - We did not have information on whether prescriptions were written to treat one or two eyes. This information would impact the duration-of-use estimations. However, based on the observation that 86% of patients in The Netherlands had surgery in only one eye and that cataract surgeries in fellow eyes are separated by a few weeks in Denmark,² we assumed that therapy episodes were for a single eye.
- The strengths of this study included the following:
 - A feasibility assessment among countries where nepafenac is prescribed identified these data sources as the most suitable data sources in Europe for the study goals.
 - Context to our findings with regard to nepafenac is provided by similar analyses of ophthalmic NSAIDs ketorolac and diclofenac.

Figure 1. Therapy Episodes of Nepafenac, Ketorolac, and Diclofenac, The Netherlands, 2009-2013

Note: The figure starts in 2009, which is the first year with complete data. Dashed lines correspond to extrapolated data for 2013 (observed data up to 31 October 2013).

Figure 2. Therapy Episodes of Nepafenac, Ketorolac, and Diclofenac, Denmark, 2009-2014

Note: The figure starts in 2009, which is the first year with complete data.

Table 1. Patient Characteristics at Baseline

Variable	Users of Study Drugs, n (%)					
	The Netherlands (2008-2013)			Denmark (2008-2014)		
	Nepafenac (n = 9,530)	Ketorolac (n = 5,351)	Diclofenac (n = 4,536)	Nepafenac (n = 60,403)	Ketorolac (n = 54,185)	Diclofenac (n = 131,440)
Age (years)						
≤ 18	27 (< 0.5)	24 (< 0.5)	35 (1)	197 (0.3)	2,038 (4)	6,231 (5)
> 18	9,503 (100)	5,327 (100)	4,501 (99)	60,206 (99.7)	52,147 (97)	125,209 (95)
Mean (SD)	71 (11)	70 (13)	70 (14)	72 (12)	63 (20)	52 (21)
Female sex	5,758 (60)	3,227 (60)	2,714 (60)	35,075 (58)	33,017 (61)	62,880 (48)
Systemic conditions						
Diabetes mellitus	1,608 (17)	786 (15)	769 (17)	7,027 (12)	3,668 (7)	6,212 (5)
Bleeding disorders	4 (< 0.5)	1 (< 0.5)	3 (< 0.5)	6 (0.0)	6 (0.0)	26 (0.0)
Charlson Comorbidity Index score $\geq 3^a$	n/a	n/a	n/a	11,941 (20)	6,235 (12)	10,000 (8)
Use of systemic medications						
Antithrombotic agents	3,738 (39)	1,838 (34)	1,638 (36)	13,916 (23)	7,576 (14)	10,874 (8)
NSAIDs	1,463 (15)	811 (15)	690 (15)	3,947 (7)	4,205 (8)	10,613 (8)
Steroids	814 (9)	393 (7)	304 (7)	2,104 (4)	2,106 (4)	3,428 (3)

n/a = not available; SD = standard deviation.

^aThe comorbidity analysis was conducted in Denmark after information regarding underrecording of cataract surgery performed in private hospitals became available; older and sicker patients were more likely to have surgery in public hospitals (where cataract surgery is recorded more reliably).

Note: Medical conditions and drug use were ascertained in the 6 months prior to the index date.

Table 2. Medical Conditions Associated With Therapy Episodes of Ophthalmic Nepafenac, Ketorolac, and Diclofenac in Adults

Variable	Therapy Episodes, n (%)					
	The Netherlands (2008-2013)			Denmark (2008-2014)		
	Nepafenac (n = 12,691)	Ketorolac (n = 7,540)	Diclofenac (n = 5,950)	Nepafenac (n = 73,648)	Ketorolac (n = 102,334)	Diclofenac (n = 184,361)
Patients aged > 18 years						
Number of episodes	12,657 (99.7)	7,508 (99.6)	5,915 (99.4)	73,411 (99.7)	99,484 (97)	177,754 (96)
Ophthalmic procedures						
Cataract surgery	2,707 (21)	1,437 (19)	916 (15)	30,450 (41)	10,951 (11)	17,885 (10)
Refractive procedures	1 (< 0.5)	1 (< 0.5)	0 (0)	5 (0.0)	180 (0.2)	2,306 (1)
Ophthalmic conditions						
Cataract	4,503 (36)	2,606 (35)	2,023 (34)	—	—	—
Dry eyes/Sjögren syndrome	8 (< 0.5)	5 (< 0.5)	8 (< 0.5)	24 (0.0)	76 (0.1)	106 (0.1)
Uveitis/iritis	13 (< 0.5)	4 (< 0.5)	5 (< 0.5)	98 (0.1)	106 (0.1)	457 (0.3)
Ophthalmic manifestations of allergy	3 (< 0.5)	4 (< 0.5)	14 (< 0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Ocular pain	7 (< 0.5)	4 (< 0.5)	8 (< 0.5)	—	—	—
Macular edema	6 (< 0.5)	2 (< 0.5)	1 (< 0.5)	14 (0.0)	33 (0.0)	46 (0.0)
Vitreous-related disorders	17 (< 0.5)	0 (0)	5 (< 0.5)	75 (0.1)	99 (0.1)	258 (0.1)
Infectious conjunctivitis	21 (< 0.5)	10 (< 0.5)	26 (< 0.5)	—	—	—
Blepharitis/stye/chalazion	21 (< 0.5)	8 (< 0.5)	5 (< 0.5)	—	—	—
Eye infection/inflammation	11 (< 0.5)	8 (< 0.5)	15 (< 0.5)	—	—	—
Ophthalmic correspondence	4,763 (38)	2,227 (30)	2,172 (37)	—	—	—
Patients aged > 18 years with Charlson Comorbidity Index score ≥ 3						
Number of episodes	—	—	—	14,997	12,570	16,888
Cataract surgery	—	—	—	6,649 (44)	2,233 (18)	3,292 (20)
Patients aged ≥ 80 years						
Number of episodes	—	—	—	19,243	22,723	23,467
Cataract surgery	—	—	—	8,552 (44)	3,277 (14)	5,186 (22)

CONCLUSIONS

- Practically all use of nepafenac is in adults.
- In both populations, less than half of the therapy episodes occurred in patients with recorded cataract surgery; however, important underrecording of cataract surgery occurs in Denmark and is likely in The Netherlands.
- Based on the dispensed number of bottles, the estimated duration of treatment is appropriate for the approved indication in 60% of adult patients without diabetes and 90% of adult patients with diabetes in The Netherlands, and in 92% and 99.8%, respectively, in Denmark.
- The underrecording of ophthalmic conditions in automated health care databases used in pharmacoepidemiology is higher than initially expected and challenges research in this important indication.

ACKNOWLEDGEMENTS

This collaborative study was conducted by RTI Health Solutions, Southern Denmark University, and PHARMO Institute under a contract with Alcon Labs, Inc., which included independent publication rights.

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