Interim and Final Study Report Template for Non-Interventional Post-Authorisation Safety Studies (PASS)

PASS INFORMATION

Title	A non-interventional, population-based register study on the prescription of etoricoxib (Arcoxia®) to dental surgery patients in the Nordic countries
Version identifier of the final study report	1.0
Date of last version of the final study report	**27-NOV-2017**
EU PAS register number	EUPAS 7134
Active substance	Etoricoxib ATC Code: M01AH05
Medicinal product	Etoricoxib (Arcoxia)
Product reference	UK/H/0532/01-04
Procedure number	UK/H/XXXX/WS/312
Marketing authorisation holder(s)	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
Joint PASS	No
Research question and objectives	Characterize dispensed etoricoxib prescribed by dentists including off-label use. The specific objectives are: • To describe dispensed etoricoxib prescribed by dentists including the associated dental procedures, patient demographics (age, gender), dosing, year, and country • To describe any dispensed etoricoxib prescribed by dentists not associated with dental procedures • To describe off-label use by dentists in patients o less than 16 years of age o with doses >90mg/day including the associated dental procedures, patient demographics (age, gender), dosing, year, and

	country • To describe, where possible, the duration of dental prescriptions, number of tablets dispensed / package size • To describe the mechanisms in place in each country, such as stickers with instructions for use to discourage use for >3 days • To describe patients who are prescribed etoricoxib who also have concurrent prescription for anti-coagulants (with the caveat that patients may have been told to hold their anti-coagulants for a few days around the dental procedure) to monitor the potential for drug interaction
Country(-ies) of study	Denmark, Finland, Norway, and Sweden
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Merck Final Repository (RCAM) Date	**27-NOV-2017**

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1 ABSTRACT

Title

A non-interventional, population-based register study on the prescription of etoricoxib (Arcoxia®) to dental surgery patients in the Nordic countries. 27th of November 2017.

PPD National Institute of Public Health, University of Southern Denmark, Øster Farimagsgade 5A, 1353 Copenhagen, Denmark

PPD

Keywords

Etoricoxib, dentalpain, dental surgery, register data, off-label use, Nordic countries**Rationale and background**

Treatment of pain associated with dental surgery is a new indication for etoricoxib (initiated in 2012). Potential risks include off-label use of etoricoxib in patients less than 16 years of age or with doses >90 mg/day or for more than 3 days. Following a request by the European Medicines and Healthcare products Regulatory Agency (MHRA), a study should be performed for the assessment of the safety of etoricoxib when prescribed in a dental surgery setting.

Research question and objectives

Characterize dispensed etoricoxib prescribed by dentists including off-label use.

The specific objectives are:

- To describe dispensed etoricoxib prescribed by dentists including the associated dental procedures, patient demographics (age, gender), dosing, year, and country
- To describe any dispensed etoricoxib prescribed by dentists not associated with dental procedures
- To describe off-label use as prescribed by dentists in patients :
  - less than 16 years of age
  - with doses >90mg/day

  including the associated dental procedures, patient demographics (age, gender), dosing, year, and country

- To describe, where possible, the duration of dental prescriptions, number of tablets dispensed / package size
- To describe the mechanisms in place in each country, such as stickers with instructions for use to discourage use for >3 days
- To describe patients who are prescribed etoricoxib who also have concurrent prescription for anti-coagulants (with the caveat that patients may have been told to hold their anti-coagulants for a few days around the dental procedure) to monitor the potential for drug interaction

Study design

A longitudinal nation-wide register-based study on etoricoxib prescriptions in dental practices including all individuals who purchased an etoricoxib prescription prescribed by dentists.

Setting

The population comprises all individuals in the four Nordic countries in the period 2012-2014 with dispensed etoricoxib prescribed by dentists.

Subjects and study size, including dropouts

No hypotheses were tested. Therefore, no sample size or power calculation were performed.

Variables and data sources

Etoricoxib prescription (date, dose strength, number of tablets dispensed, etc.), dental procedures (type and date), and patient demographics (age and gender).

Results

Overall, 1278 prescriptions of etoricoxib prescribed by a dentist were redeemed in Denmark, Finland and Sweden from 2012-2014. Data from Norway only included prescription redemptions with no information about dental procedures, and was analysed separately. Overall, 337 prescriptions of etoricoxib prescribed by a dentist were redeemed in Norway from 2012-2014.

For Denmark, Finland, and Sweden, a total of 33.4% of the prescription redemptions were to individuals with no registered dental procedure, 29.9% of the prescription redemptions had a contemporaneous link to a dental procedure, defined as a prescription redeemed in the time frame of two weeks before to one week after the dental procedure, and 37.7% of the prescription redemptions had a procedure, but it was outside that time frame.

According to the regulations at the national statistical bureaus it is not allowed to present results for less than three individuals so in some cases, exact data or percentages are not provided. There were <3 etoricoxib prescription redemptions with a recorded age <16 years. A total of 42.3% of the prescription redemptions in Denmark, Finland, and Sweden were for 120 mg tablets. A total of 57.9% of the dental prescriptions in Norway were for 120 mg tablets.

Less than 22 individuals with etoricoxib prescription redemptions had an anti-coagulant prescription redemption within the prior 90 days in Sweden.

Discussion

The overall utilization of etoricoxib for dental pain was quite low. Over the 3 year period from 2012-2014, there were a total of 1615 redemptions of prescriptions written by dentists in Denmark, Sweden, Finland and Norway. The study demonstrated heterogeneity across countries in the prescription of etoricoxib by dentists.

Unexpectedly, only 30% of the prescription redemptions for Denmark, Finland, and Sweden had a contemporaneous link to a dental procedure. One possible explanation is that dentists may be prescribing etoricoxib for dental pain not associated with a specific procedure.

There were <3 etoricoxib prescription redemptions with a recorded age <16 years over the 3 year study period. Thus off-label use in this population appears to be limited.

A total of 42.3% of the prescription redemptions were for >90 mg tablets in Denmark, Finland and Sweden (specifically for 120 mg tablets). A total of 57.9% of the prescriptions were for >90 mg tablets in Norway. National experts consulted on this study have not been able to provide an explanation for the relatively high proportion of prescriptions redemptions for >90 mg tablets. They note that national guidelines are consistent with the etoricoxib label and recommend a dose of 90 mg once daily for up to three days for pain associated with dental procedures.

Given that the minimum package sizes in the Nordic countries range from 2 to 28 tablet blister packs, it is not possible to ascertain how much off label use lasting >3 days actually occurs.

Limitations of the study include the information available from the registers to ascertain off-label use is limited. There is no direct information on the reason for etoricoxib prescriptions and no information on the instructions for use given to the patients on the package sticker in terms of number of days to take etoricoxib.

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2 LIST OF ABBREVIATIONS

ApEHR	Institute of Applied Economics and Health Research
ATC	Anatomical Therapeutic Classification
CPR	Unique personal identification number (CPR number)
EMA	European Medicines Agency
EU	The European Union
FDA	US Food and Drug Administration
MHRA	Medicines and Healthcare products Regulatory Agency
NIPH	National Institute of Public Health, University of Southern Denmark
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over the counter
REK	Regional Ethics Committee, Norway
THL	National Institute for Health and Welfare, Finland

3 INVESTIGATORS

Principal investigator	PPD **Denmark** Role: Acquisition and procurement of national Danish data. Responsible for statistical analysis and for the storing and reception of data from all countries: Data management, data analysis, and reporting. PPD Denmark PPD
Academic Research Organization	**Institute of Applied Economics and Health Research** Role: Project management and cross country coordination, contact to Merck & Co, development of the study protocol, scientific responsibility for the study including analytical advice, coordination of involvement of the national scientific coordinators as well as the experts. ▪ PPD ▪ PPD Odense University Hospital and University of Southern Denmark
National scientific coordinators	Role: Acquisition and procurement of national data including analytical and scientific advice. ▪ Sweden: PPD Nationalekonomiska Institutionen, Department of Economics, School of Economics and Management, Lund University ▪ Finland: PPD Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki and Professor in Epidemiology, School of Health Sciences, University of Tampere ▪ Norway: PPD University of Oslo, Norway and PPD Institute of Public Health, University of Southern Denmark, Odense ▪ Denmark: PPD National Institute of Public Health, University of Southern Denmark, Øster Farimagsgade 5A, 1353 Copenhagen, Denmark
Sponsor contacts	PPD Merck Project Director PPD Merck Study Manager

4 OTHER RESPONSIBLE PARTIES

Additional Investigators	PPD **Denmark** Role: Acquisition and procurement of national Danish data. Responsible for statistical analysis and for the storing and reception of data from all countries: Data management, data analysis, and reporting. ▪ PPD ▪ PPD
Additional Investigators	PPD Role: Project management and cross country coordination, contact to Merck & Co, development of the study protocol, scientific responsibility for the study including analytical advice, coordination of involvement of the national scientific coordinators as well as the experts. ▪ PPD
Expert dental consultants	Role: Advise regarding the development of the protocol, the study design, the analyses, and the results ▪ Finland: PPD Operational Control (OPER). Information Services. Department of Health and Welfare. PL 30, 00271 Helsinki, Finland ▪ Sweden: PPD Faculty of Odontology. Malmö University, Sweden ▪ Sweden: PPD Futurum Clinic. Faculty of Odontology. Malmö University, Sweden ▪ Denmark: PPD Faculty of Odontology, University of Copenhagen, Denmark ▪ Norway: PPD University of Oslo, Norway

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Protocol approval	31-JUL 2014	23-JUL-2014	
Start of data collection	01-JUL-2014	01-JUL-2014	
Registration in the EU PAS register	15-AUG-2014	15-AUG-2014	
End of data collection	24-NOV-2014	09-DEC-2016	Due to long waiting periods for data extraction in Finland the data collection process was markedly prolonged.
End of data analysis	05-JAN-2015	30-MAY-2017	
Feedback received from dental experts	N/A	05-JUL-2017	Due to unexpected findings, feedback from dental experts was requested.
Final report of study results	30-SEP-2015	27-NOV-2017	The delay in the data collection process resulted in a corresponding delay in data analysis and reporting.

6 RATIONALE AND BACKGROUND

Etoricoxib is a selective COX-2 inhibitor belonging to the non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are commonly prescribed in dental practice for the management of pain and swelling [Ref. 5.4: 04QFJ9]. Etoricoxib was originally approved in 2002. It is marketed under several trade names such as Arcoxia, Algix, Tanxib, Nocoxia, and Etorix. Etoricoxib is indicated for the symptomatic relief of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, the pain and signs of inflammation associated with acute gouty arthritis, and as of 2012, for short-term treatment of moderate pain associated with dental surgery. For the treatment of moderate pain associated with dental surgery, "the recommended dose is 90 mg once daily, limited to a maximum of 3 days" [http://www.medicines.org.uk/emc/medicine/29136#POSOLOGY]. Labeling also indicates "some patients may require additional postoperative analgesia" (i.e., rescue therapy during etoricoxib treatment). Etoricoxib is contraindicated in "Children and adolescents under 16 years of age" [http://www.medicines.org.uk/emc/medicine/29136#CONTRAINDICATIONS].

Etoricoxib is available as 30, 60, 90, and 120 mg tablets. The Anatomical Therapeutic Classification (ATC) code is M01AH05.

Treatment of pain associated with dental surgery is a new indication for etoricoxib (2012). Potential risks include off-label use of etoricoxib in patients less than 16 years of age. Following a request by the European Medicines and Healthcare products Regulatory Agency (MHRA), a study should be performed to characterize off-label use in the dental surgery setting, including paediatric use.

To assess the use of etoricoxib, detailed information on prescriptions for post-operative dental pain will be obtained from the national registers in Denmark, Finland, Norway, and Sweden on an individual basis. The dental surgery procedure(s) that are carried out on the patient, which are associated with the prescription of etoricoxib for post-operative pain will also be obtained, as applicable. Finally, in order to record possible prescribing to people under the age of 16, the age and gender of the patients receiving etoricoxib will be analyzed. Due to general reimbursement of dispensed NSAIDs and the majority of necessary health care procedures, data on dispensed dental prescriptions of etoricoxib, and most dental procedures are available in all four countries.

Very little is known about the use of etoricoxib among dentists, and no specific data is available about the use in Nordic countries. A reasonable estimate is less than 500 prescriptions per year for the Nordic countries. There is currently no published information on dental use of etoricoxib and dental off-label use. Consequently, a total population study is necessary in order to evaluate use of etoricoxib and specifically if there is off-label use of etoricoxib by dentists. Dental prescription of etoricoxib may be considered off-label in people under 16 years of age or if doses > 90 mg/day are prescribed. Duration of treatment cannot be assessed because the instructions to the patient about duration of use are not consistently available across the Nordic region, and the packaging of etoricoxib may include supplies for more than 3 days treatment. The minimum package sizes in the Nordic

countries are 2, 5, 7, and 28 tablets in Denmark, Finland, Norway, and Sweden, respectively. Etoricoxib is packaged in blister packs.

The Nordic health and prescription registers contain information needed to perform an analysis to meet the above objectives. In 2011, approximately 3 million total dispensed prescriptions for NSAIDS were issued in the Nordic countries combined. In Finland, in 2011 a total of 300,000 dispensed prescriptions of COX-2 inhibitors were issued. Each of the 5150 dentists in Finland write on average about 87 prescriptions per year. Approximately 100,000 of these dispensed prescriptions were for NSAIDs.

http://www.medicines.org.uk/emc/medicine/29136#CONTRAINDICATIONS

www.medstat.dk

http://www.norpd.no/

http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel

http://www.kela.fi/web/en/statistical-database-kelasto

Data from the Danish National Prescription Register [www.medstat.dk] indicate that about 8,778 and 13,071 Danish citizens were dispensed prescriptions for etoricoxib by a prescription at least once annually in 2003 and 2004, respectively. The number of Danish citizens who were dispensed prescriptions for etoricoxib at least once decreased to 1,663 and 1,284 individuals in 2011 and 2012, respectively. The annual number of Danish children (age 0-14 years) who were dispensed a prescription for etoricoxib at least once ranged from 0-8 children in 2003-2012, in 2011-2012, no children (0-14 years) were prescribed etoricoxib.

Off-label usage of NSAIDs has been analyzed in several studies, especially among neonates and infants in hospital wards. From Table 2 the frequency of off-label usage in children in Swedish hospitals is described. In total, 41% of all authorized drugs were given off-label and the highest proportion of off-label prescriptions occurred in neonates and infants in intensive care [Ref. 5.4: 04QFJB]. Off-label drug prescriptions in hospitals vary considerably among ATC-groups. According to Table 2 the largest number of off-label drug prescriptions is found among drugs for the nervous system (N), analgesics (mostly paracetamol), blood and blood-forming organs (B), and the alimentary tract and metabolism (A). The highest proportion of off-label classification was found among drugs for the eye (S), for the skin (D), and drugs for blood or blood-forming organs (B). The NSAID diclofenac was prescribed in 2.1% of the off-label pediatric cases.

Table 2 The most commonly prescribed approved drugs used off-label in hospitalized Swedish children (Sweden 2011) [Ref. 5.4: 04QFJB]

3879 off-label prescriptions in 2947 children of totally 11,294 prescriptions= 34%		(n=3879)	
Substances	ATC	Number	%
Carbohydrates	B	479	12.3
Electrolytes +/- carbohydrates	B	341	8.8
Paracetamol	N	320	8.2
Sodium chloride	B	113	2.9
Epinephrine	C	103	2.7
Morphine	N	102	2.6
Midazolam	N	87	2.2
Sulfamethoxazole/trimethoprim	J	84	2.2
Diclofenac	M	83	2.1
Heparin	B	81	2.1

7 RESEARCH QUESTION AND OBJECTIVES

Characterize dispensed etoricoxib prescribed by dentists including off-label use.

The specific objectives are:

- To describe dispensed etoricoxib prescribed by dentists including the associated dental procedures, patient demographics (age, gender), dosing, year, and country
- To describe any dispensed etoricoxib prescribed by dentists not associated with dental procedures
- To describe off-label use as prescribed by dentists in patients :
  - less than 16 years of age
  - with doses >90mg/day

  including the associated dental procedures, patient demographics (age, gender), dosing, year, and country
- To describe, where possible, the duration of dental prescriptions, number of tablets dispensed / package size
- To describe the mechanisms in place in each country, such as stickers with instructions for use to discourage use for >3 days
- To describe patients who are prescribed etoricoxib who also have concurrent prescription for anti-coagulants (with the caveat that patients may have been told to hold their anti-coagulants for a few days around the dental procedure) to monitor the potential for drug interaction

The study is a descriptive analysis of the use of etoricoxib prescribed by dentists. No hypothesis will be tested.

8 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	15-JAN-2015	Results	Update	Data on dental procedures performed in individuals who redeemed an etoricoxib prescription were not available for the study in Norway. Therefore, all analyses have been performed for Denmark, Finland and Sweden without including data from Norway. Data from Norway regarding etoricoxib prescriptions are analysed and presented separately.
2	09-DEC-2016	Results	Update	Prescription redemptions of anti-coagulants in Finland were not available for the study. The analysis of potential drug interaction between etoricoxib and anti-coagulants (i.e. patients who are prescribed etoricoxib who also have concurrent prescriptions for anti-coagulants) is limited to Denmark and Sweden.
3	02-JUN-2017	Results	Update	Due to a small number of prescription redemptions in some of the age groups, the age groups were changed from 5-year age groups to 10-year age groups.
4	02-JUN-2017	Research Methods	Update	To evaluate the effect of the selected time frame for the definition of a clear linkage between an etoricoxib prescription redemption and a dental procedure, the time frame was modified to four weeks before to two weeks after a dental procedure as a sensitivity analysis.

9 RESEARCH METHODS

9.1 Study design

A non-interventional, population-based study of dispensed etoricoxib prescriptions in dental practice in the Nordic countries will be performed using prescription register data.

A longitudinal study design will be used including all individuals who receive a dispensed etoricoxib prescription prescribed by dentists in the period 2012-2014. In order to ensure adequate data to address the off-label use questions, the national registers from all four Nordic countries will be used for study.

No hypothesis is tested and therefore, no sample size calculation has been performed.

Data on dispensed etoricoxib prescriptions by dentists will be made available from the national prescription drug registers in all four countries. The dispensed dental prescriptions will be linked with data on performed dental procedures on an individual level, based on reimbursement data from national health services registers. The use of etoricoxib for dental surgery in hospital wards is minimal, but inpatient procedures will be included.

For completeness, if dispensed prescriptions of etoricoxib not associated with a dental surgery procedure are identified in the registers, these prescriptions will still be noted and analyzed. The claim may not have been posted by the dentist or the prescription may have been used for non-surgical dental pain (e.g., in the context of an infection (dental abscess) being treated medically with antibiotics and analgesia).

9.2 Setting

The study population consists of all individuals who purchased etoricoxib prescribed by dentists. Because the dental pain indication for etoricoxib was approved for use in the EU in 2012, the study period is 2012-2014 for all four countries. The national prescription and health services registers in the Nordic countries enable this study to cover the whole population of individuals with an etoricoxib prescription by dentists and ensures valid estimates for the Nordic countries.

The study will cover all prescriptions of etoricoxib purchased at a pharmacy (dispensed and paid for) and prescribed by dentists, since these are the only prescriptions tracked in the national prescription registers. Etoricoxib that is handed directly to the patients in hospital wards or by the dentists will not be included. Prescriptions that have not been used, because the patient, for whatever reason, decides not to collect the drugs in the pharmacy, are not included in this study. Etoricoxib is not available over the counter (OTC).

9.3 Subjects

The study population comprises individuals in Denmark, Finland, Norway, and Sweden with dispensed etoricoxib prescribed by dentists and purchased from 2012 to 2014.

9.4 Variables

Table 9.4a includes information on the variables available from the four countries, which were used to construct the dataset for analysis.

Table 9.4a Variables available from the four countries

Variable
Personal identification number (encrypted)
Gender
ATC code (for etoricoxib and anti-coagulants)
Date of prescription redemption
Type of prescriber (i.e. dentist, other) of etoricoxib
Prescriber identification number
Age at prescription redemption
Dose
Package size
Number of packages
Type of dental procedure#
Date of dental procedure#
Dentist identification number performing dental procedures#

Not available in dataset from Norway

The dental procedures were extracted from the national health services registers in Denmark, Sweden, and Finland. The procedure codes vary between the Nordic countries. A list of procedure codes is provided in Table 9.4b. The specific codes were identified by dentists in each country familiar with the relevant coding systems.

Table 9.4b Dental surgery procedures and national dental reimbursement codes (Table 5 in the protocol)

	Dental procedure codes					
	Denmark		Sweden		Norway†	Finland
	Health Service Register	National Patient Register	Dental register	Patient register		Hilmo (care registers for social welfare and health care) and Kela (pharmaceutical register)
Dental cavity fillings without pulp communication	1501-1559	BEOA0-BEOA6	701-708, 321-322	TEB10 TEB20	201-207	SCE00 (fissure sealant), SFA 00,10,30,40 (cavity filling by direct method, codes SFB10,20,30,40 are used when the filling is made by dental laboratory or otherwise indirectly, for example laminates)
Pulp capping	1600	BEOB0	521	TEB30		SGC10
Coronal amputation of pulp	1601	BEOB1		TEB30		SGB00
Opening to pulp and canal cleaning	1605	BEOB2	501-504, 522	TEB30 TEB40	210-212	SGA01-6 (used when removing for example broken treatment equipment from the canal)
Apical amputation	1606	KEBA30-KEBA40	541-542	EBA40	406-409	EBA40, 45
Extraction of tooth	1701	KEBA00A - KEBA00B	401-403	EBA00	401-402	EBA00,05,15 (EBA 15 is used when extracting at least 4 teeth from the same jaw at the same visit)
Surgical removal of tooth	1801	KEBA10-KEBA99	404-406	EBA10 EBA99	403-405	EBA10,12,20,30 (EBA20 is used when extracting one root of tooth with many roots, EBA30 is used when extracting remaining root)
Treatment of bleeding after extraction	1705	KEWD00-KEWE00	480			No specific code
Periodontal treatment	1420 1425	BEXC0	341		501	SDA01-5 SDE02-3 (used by dental hygienist)
Expanded periodontal treatment	1430	KECA10	342-343		503-505	SDA12-14

Scaling of teeth*	1301 1302	BEXC0				Scaling of teeth and root surfaces are included in all periodontal treatments (SD: "Treatment of gums and periodontal diseases"). Codes SDA01-05 and SDE02-04 are related to time spent in procedure, and codes SDA12-14 are related to diagnose of periodontal disease
Scaling of root surfaces**	1431	BEOB0				See above
Surgical periodontal treatment	1440	KECA15	441-445	EBA30 ECA40 ECA50	502,514, 516-517	ECA50,55
Surgical measures - implant treatment etc.	Implant treatment consist of a surgical part (coding 1801) and a prosthetic part (no coding- not reimbursed – free pricing)	KECD00	420-430, 435-436	EBB10 EBB15 EEC42 EEC45 EEU00 EFU00	412-423, 410-420	ECW05 (setting of mini-implants) EBB10,11,15 (setting of implants) ECU00 (removing of implant) ECU05,06 (removing of mini-implant)
Prosthetic measures	No reimburse-ment of these services so no coding – free price area	BEDA0-BEDA8	800-809, 811-815, 822-829, 831-839, 850 852-857, 861-865, 871-878	TEB00	301-315	SPA00,05,10 (pre-treatment measures) SPA10,20 (implants) SPB00,10,15,20,25,28,30 (temporary crowns and bridges) SPC10,20,25,30,35,40,45 (crowns and bridges) SPC50 (root canal post made by lab) SPD00,05,10,20 (removable full dentures) SPE00,05,10,90 (removable partial dentures) SPF00,10,20,30,40,50,60 (repairing measures)

*, **: Often part of periodontal treatment
†Codes were identified for Norway; however, no procedure data were provided

9.4.1 Exposure

The current study is a descriptive analysis of etoricoxib prescription redemptions by dentist, linkage with dental procedures and off-label use. There is no exposure in the present study.

9.4.2 Outcome

The current study is a descriptive analysis of etoricoxib prescription redemptions by dentist, linkage with dental procedures and off-label use. There are no outcomes in the present study.

9.4.3 Covariates

No covariates in the present study.

9.5 Data sources and measurement

The ability to perform register-based research is driven by the unique personal identification number (CPR number) introduced in the Nordic countries in the 1960's and available to all persons with permanent residence in the Nordic countries [Ref. 5.4: 03N0P3]. The CPR number makes it possible to link information at the individual level from several registers for scientific research purposes [Ref. 5.4: 04QFJD, 00W4D0]. According to the Danish Act on Processing of Personal Data (and similar privacy regulations in the other Nordic countries), when working with individual level data, confidentiality and full anonymity for the data subjects should be provided. When data are provided by the registers, the personal identification number is anonymised in a way that makes linkage possible, but makes it impossible to identify individuals.

In addition, individual level data from Statistics Denmark are not delivered to any external firm, institution, or person. Instead, datasets and linkages between datasets constructed at Statistics Denmark are stored at Statistics Denmark. Researchers employed at specific authorised institutions can establish remote online access to these datasets stored at Statistics Denmark.

Although researchers may get access to rather detailed individual level data, they are only allowed to publish statistical analyses and results at an aggregated level where no single person or enterprise may be identified. Counts with less than three individuals are not allowed to be tabulated.

For security reasons, only researchers employed at authorised research institutions can get access to individual-level data at Statistics Denmark.

The national prescription and health services registers within each of the Nordic countries capture all the individual encounters of purchasing etoricoxib prescribed by dentists and the dental procedures performed. The registers cover different periods (Table 9.5a), but all registers have information for the period 2012-2014.

Table 9.5a National health registers in the Nordic countries of relevance for the present study including registration period

Register	Country			
	Denmark	Finland	Norway	Sweden
National prescription register	1995-2014	1994-2014	2004-2014	2005-2014
National health service register	1990-2014	2011-2014	2006-2014	2001-2014
National patient register	1977-2014	1967-2014	2008-2014	1987-2014
Civil registration system	1968-2014	1967-2014	1964-2014	1965-2014
Study period	2012-2014	2012-2014	2012-2014	2012-2014

For Denmark, Statistics Denmark gave access to four relevant datasets: Prescription Register (with prescription redemptions of etoricoxib prescribed by a dentist and anticoagulants), Health Service Register, National Patient Register, and Civil Registration System.

For Finland and Sweden, access was given to four datasets from the registers: Prescription Register (with prescription redemptions of etoricoxib and anticoagulants for Sweden and for etoricoxib for Finland), Health Service Register, National Patient Register and Civil Registration Register.

For Norway, one dataset was delivered: etoricoxib from the Prescription Register. Due to data access restrictions, no other data were provided for Norway.

9.5.1 Study Procedures

This was a database study using data extracted from national registers. See sections 9.1 – 9.5 above and 9.8 and 9.9 below for study procedures.

9.6 Bias

Not applicable.

9.7 Study size

The study included all patients with a dispensed prescription for etoricoxib prescribed by a dentist in Denmark, Sweden, Finland, and Norway from 2012-2014. Because the analyses were strictly descriptive, no sample size calculations were done.

9.8 Data transformation

Not applicable.

9.8.1 Data management

The handling of data in the etoricoxib study involved five steps. The primary scientific coordinator from Denmark was responsible for the overall study and establishment of the joint Nordic data set. The Finnish, Norwegian, and Swedish national scientific coordinators were responsible for steps 1-3 in each country (explained below), and the primary scientific coordinator was responsible for steps 1-3 for Denmark and 4-5 for all countries.

The handling of data followed the five steps outlined below:

1. All national scientific coordinators submitted applications to the relevant authorities and agencies for permission to perform the study and to get access to data, including Statistics Denmark/Statistics Finland/Statistics Norway/Statistics Sweden and relevant health authorities to search the national prescription registers for all dispensed etoricoxib prescribed by dentists.
2. Each national scientific coordinator facilitated the construction of the national study populations, consisting of:
   - all etoricoxib users (i.e. prescription redemptions) and prescriptions during the study period 2012-2014 prescribed by dentists (Denmark, Sweden, Finland, and Norway)
   - all anticoagulant prescription redemptions during the study period 2012-2014 (Denmark & Sweden only)
   - the associated dental procedures performed either on an outpatient or inpatient basis (Denmark, Sweden, and Finland)
   - patient demographics.

- Each national scientific coordinator was responsible for acquiring and validating the data sets.
- Data extraction for each country was done as described below:
- All etoricoxib users were extracted from the national prescription registers for 2012-2014. The dental procedures and patient demographics for the etoricoxib users (identified by encrypted CPR numbers) were extracted from the health service registers, the national patient registers, and the civil registration systems for all countries except Norway.
- Data validation and quality control of data included the following:
  - checks for valid values for each categorical variable using frequency distributions,
  - checks for consistency between dates (Date of birth before all other dates and date of death after all dates)
  - checks for missing data
- Each national scientific coordinator produced a document describing the checks performed.

3. The datasets from Finland, Norway, and Sweden were transferred to ApEHR, who further transferred data to Statistics Denmark where all subsequent data handling was done by the Danish scientific coordinator / primary study coordinator.

4. The primary study coordinator linked data for each country separately, and then data sets from all countries were combined into one data set for the analysis.
5. The primary study coordinator assessed the data validity of the combined data set from all countries by logic checks and examination of extreme values and missing data.

   The steps 4-5 were performed on servers of Statistics Denmark. The programming was performed by two independent researchers to ensure high programming quality. The statistical programs were stored at the servers on Statistics Denmark

9.9 Statistical methods

9.9.1 Main summary measures

Descriptive analyses were performed for each of the objectives.

The distribution of etoricoxib prescription redemptions prescribed by a dentist during the period from 2012 to 2014 was performed by means of frequencies (number of prescription redemptions and percentages). The descriptive analysis was performed overall and stratified by gender, age group, year of prescription redemption, country, dose and number of tablets.

The distribution of etoricoxib prescription redemptions prescribed by a dentist during the period from 2012 to 2014 in total and among individuals with and without a dental procedure was performed by means of frequencies (number of prescription redemptions and percentages). The descriptive analysis was performed overall and stratified by gender, age group, year of prescription redemption, country, dose and number of tablets. The analysis was performed for those with a contemporaneous link to a dental procedure, without a contemporaneous link to a dental procedure, and without any procedure. A prescription redemption with a contemporaneous link to a dental procedure was defined as an etoricoxib prescription redeemed in the time frame of two weeks before to one week after a dental procedure. An etoricoxib prescription redemption without a contemporaneous link to a dental procedure was an etoricoxib prescription redemption occurring outside this time frame. See section 9.9.4 below regarding sensitivity analysis on the period for a contemporaneous link to a dental procedure.

The distribution of use of etoricoxib >90 mg tablets prescribed by a dentist with and without a contemporaneous link to a dental procedure during the period from 2012 to 2014 was performed by means of frequencies (number of prescription redemptions and percentages). The descriptive analysis was performed overall and stratified by gender, age group, year of prescription redemption, country, dose, and number of tablets.

The distribution of individuals with overlapping prescription redemptions of etoricoxib prescribed by a dentist and anti-coagulants was performed by means of frequency distributions. Varying periods of prescription overlap were considered (0-14 days, 15-29 days, 30-59 days, and 60-90 days).

9.9.2 Main statistical methods

All analyses were descriptive. See section 9.9.1 above.

9.9.3 Missing values

No missing data was present in data extracted for the study.

9.9.4 Sensitivity analyses

The time frame for the definition of a contemporaneous linkage between an etoricoxib prescription redemption and a dental procedure was defined as an etoricoxib prescription redeemed in the time frame of two weeks before to one week after a dental procedure. To evaluate the effect of the selected time frame for the definition of a contemporaneous linkage between an etoricoxib prescription redemption and a dental procedure the time frame was modified to four weeks before to two weeks after a dental procedure.

9.9.5 Amendments to the statistical analysis plan

Due to data access restrictions, data on dental procedures performed in individuals who redeemed an etoricoxib prescription were not available for the study in Norway. Therefore, all analyses have been performed for Denmark, Finland and Sweden without including data from Norway. Data from Norway regarding etoricoxib prescriptions are analysed and presented separately.

Prescription redemptions of anti-coagulants in Finland were not available for the study. The analysis of potential drug interaction between etoricoxib and anti-coagulants (i.e. patients who are prescribed etoricoxib who also have concurrent prescriptions for anti-coagulants) is limited to Denmark and Sweden.

Due to a small number of prescription redemptions in some of the age groups, the age groups were changed from 5-year age groups to 10-year age groups.

The sensitivity analysis using a wider time frame for the linkage of prescriptions and dental procedures was added.

9.10 Quality control

See section 9.8.1.

10 RESULTS

According to the regulations at the national statistical bureaus, it is not allowed to present results for less than three individuals, so for some tables, exact data or percentages are not provided.

10.1 Participants

Overall, 1278 prescription redemptions of etoricoxib among adults (≥16 years of age) prescribed by a dentist were included in the study from Denmark, Finland and Sweden, 2012-2014 (Table 10.2a). Only 12 etoricoxib prescriptions written by dentists were dispensed in Denmark over the study period. There were <3 etoricoxib prescription redemptions with a recorded age <16 years. Results for children (age <16 years) are therefore not included in the tables.

Data from Norway included only etoricoxib prescription redemptions with no information about dental procedures, and was handled separately. A total of 337 etoricoxib prescription redemptions were prescribed by a dentist in Norway, 2012-2014 (Table 10.2b). No children had etoricoxib prescription redemptions in Norway.

10.1.1 Protection of Human Subjects

The study was approved by the Danish Data Protection Agency. According to the Danish legislation, no further approval is needed for register-based studies without contact to study participants.

The study was approved by the Finnish Data Protection Agency. According to the Finnish legislation, no further approval is needed for register-based studies without contact to study participants.

The study was approved by the Regional Committees for Medical and Health Research Ethics (REK) according to Norwegian legislation.

The study was approved by the Swedish Regional Ethical Board in Lund. According to Swedish legislation no further approval is needed for register-based studies that do not involve any contact with individual study participants."

10.2 Descriptive data

Description of dispensed etoricoxib prescribed by dentists including the associated dental procedures, patient demographics (age, gender), dosing, year, and country

For Denmark, Sweden, and Finland, a total of 56.6% of the prescriptions were redeemed by women (Table 10.2a) with 62.9% redeemed by women in Norway (Table 10.2b). The number of prescription redemptions was similar across the three years 2012-2014. The recommended dose is 90 mg daily; however, 42.3% and 57.9% of the prescriptions were for 120 mg tablets in Denmark, Sweden, and Finland (combined) and Norway respectively. Three quarters (76.2%) of prescription redemptions in Denmark, Sweden, and Finland were for numbers of tablets consistent with the minimum package sizes (7-28 tablets) with 23.8% of prescriptions for ≥30 tablets. For Norway, 60.2% of the prescriptions were for 7 tablets, 27.9% for 28 tablets, and only 2.1% for ≥30 tablets.

Table 10.2a Distribution of etoricoxib prescription redemptions prescribed by a dentist during the period from 2012-2014

		Number and % of prescription redemptions
Overall		1278
Gender	Female	724 (56.6%)
	Male	554 (43.4%)
Age group at prescription redemption	16-25	121 (9.5%)
	26-35	181 (14.2%)
	36-45	198 (15.5%)
	46-55	277 (21.7%)
	56-65	330 (25.8%)
	66-75	120 (9.4%)
	>75	51 4.0%)
Year at prescription redemption	2012	395 (30.9%)
	2013	464 (36.3%)
	2014	419 (32.8%)
Country	Denmark	12 (0.9%)
	Sweden	359 (28.1%)
	Finland	907 (71.0%)
	Norway†	-
Dose (mg/tablet)	30 mg	103 (8.1%)
	60 mg	284 (22.2%)
	90 mg	350 (27.4%)
	120 mg	541 (42.3%)
Number of tablets	7	403 (31.5%)
	14	57 (4.5%)
	21	5 (0.4%)
	28	509 (39.8%)
	≥30	304 (23.8%)

†Because only etoricoxib prescription redemption data were available for Norway, these data are provided in table 10.2b and the remaining tables only provide data for Denmark, Sweden, and Finland.

Table 10.2b Distribution of etoricoxib prescription redemptions prescribed by a dentist during the period from 2012-2014 in Norway

		Number and % of prescription redemptions
Overall		337
Gender	Female	212 (62.9%)
	Male	125 (37.1%)
Age group at prescription redemption	0-15	0 (0%)
	16-25	28 (8.3%)
	26-35	52 (15.4%)
	36-45	97 (28.8%)
	46-55	76 (22.6%)
	56-65	44 (13.1%)
	66-75	18 (5.3%)
	>75	22 (6.5%)
Age at prescription redemption	<16	0 (0%)
	≥16	337 (100%)
Year at prescription redemption	2012	100 (29.7%)
	2013	129 (38.3%)
	2014	108 (32.1%)
Dose (mg/tablet)	30	28 (8.3%)
	60	18 (5.3%)
	90	96 (28.5%)
	120	195 (57.9%)
Number of tablets	<7	<3 (-)
	7	203 (60.2%)
	14	31 (9.2%)
	28	94 (27.9%)
	≥30	7 (2.1%)

Two thirds (66.6%) of the etoricoxib dental prescription redemptions had one or more dental procedures at any time during the study period with similar proportions over the 3 years (Table 10.2c). For Denmark, Sweden, and Finland, 100%, 42.6%, and 75.6% of the prescription redemptions had a procedure during the study period. Of the prescription redemptions for 30-90 mg tablets, 58-59% had a procedure during the study period while 72.4% of the prescription redemptions for 120 mg tablets had a procedure.

Only 40.1% of prescription redemptions with 30 or more tablets had a dental procedure, as compared to more than 70% for the lower numbers of tablets.

Table 10.2c Distribution of prescription redemptions with one or more dental procedures in individuals (≥16 years of age) redeeming etoricoxib prescribed by a dentist

		Number of prescription redemptions N	Dental procedures* N (Row % (% of total prescription redemptions for subgroup))
Overall		1278	852 (66.6%)
Gender	Female	724	462 (63.8%)
	Male	554	389 (70.2%)
Age group at prescription redemption	16-25	121	58 (47.9%)
	26-35	181	134 (74.0%)
	36-45	198	132 (66.7%)
	46-55	277	184 (66.4%)
	56-65	330	214 (64.9%)
	66-75	120	92 (76.7%)
	>75	51	37 (72.6%)
Year at prescription redemption	2012	395	262 (66.3%)
	2013	464	295 (63.6%)
	2014	419	294 (70.2%)
Country	Denmark	12	12 (100%)
	Sweden	359	153 (42.6%)
	Finland	907	686 (75.6%)
Dose (mg/tablet)	30 mg	103	61 (59.2%)
	60 mg	284	164 (57.8%)
	90 mg	350	202 (57.7%)
	120 mg	541	424 (72.4%)
Number of tablets	7	403	323 (80.2%)
	14	57	41 (71.9%)
	21	5	5 (100%)
	28	509	360 (70.7%)
	≥30	304	122 (40.1%)

*Relevant dental procedures are specified in the protocol Table 5. Dental procedure per prescription is counted as one if the person has one or more dental procedures any time during the study period.

A total of 29.9% of the prescription redemptions of etoricoxib had a contemporaneous link to a dental procedure and 36.7% of prescription redemptions had a dental procedure, but without a contemporaneous link. A prescription was considered linked to a dental procedure if it was redeemed in the time frame of two weeks before to one week after the procedure. An etoricoxib prescription redemption without a contemporaneous link to a dental procedure was an etoricoxib prescription redemption occurring outside this time frame. Finally, 33.4% of all prescription redemptions were not associated with a dental procedure at any time during the study period. (Table 10.2d)

Prescription redemptions in Sweden were less likely to have a clear contemporaneous link to a dental procedure (6.7%) than prescription redemptions in Denmark and Finland (50.0% and

38.8% respectively). Prescription redemptions for 120 mg tablets were more likely to have a contemporaneous link to a dental procedure (44.7%) than prescriptions for other doses (15-24%). (Table 10.2d)

Table 10.2d Distribution of etoricoxib prescription redemptions prescribed by a dentist during the period from 2012-2014 in total and with and without a dental procedure

		Prescription redemptions in total	Prescription redemptions with a dental procedure		Prescription redemptions without a dental procedure
		N	Prescription redemptions with a contemporaneous link to a dental procedure* N (row % of total)	Prescription redemptions without a contemporaneous link to a dental procedure* N (row % of total)	N (row % of total)
Overall		1278	382 (29.9%)	469 (36.7%)	427 (33.4%)
Gender	Female	724	190 (26.2%)	272 (37.6%)	262 (36.2%)
	Male	554	192 (34.7%)	197 (35.6%)	165 (29.7%)
Age group at prescription redemption	0-15	<3 (-)	<3 (-)	<3 (-)	<3 (-)
	16-25	121	41 (33.9%)	17 (14.0%)	63 (52.1%)
	26-35	181	81 (44.8%)	53 (29.3%)	47 (26.0%)
	36-45	198	61 (30.8%)	71 (35.9%)	66 (33.3%)
	46-55	277	69 (24.9%)	115 (41.5%)	93 (33.6%)
	56-65	330	80 (24.2%)	134 (40.6%)	116 (35.2%)
	66-75	120	41 (34.2%)	51 (42.5%)	28 (23.3%)
	>75	51	9 (17.6%)	28 (54.9%)	14 (27.5%)
Year at prescription redemption	2012	395	119 (30.1%)	143 (36.2%)	133 (33.7%)
	2013	464	114 (24.6%)	181 (39.0%)	169 (36.4%)
	2014	419	149 (29.8%)	145 (34.6%)	125 (29.8%)
Country	Denmark	12	6 (50.0%)	6 (50.0%)	0 (0.0%)
	Sweden	359	24 (6.7%)	129 (35.9%)	206 (57.4%)
	Finland	907	352 (38.8%)	334 (36.8%)	221 (24.3%)
Dose (mg/ tablet)	30	103	25 (24.3%)	36 (35.0%)	42 (40.8%)
	60	284	43 (15.1%)	121 (42.6%)	120 (42.3%)
	90	350	72 (20.6%)	130 (37.1%)	148 (42.3%)
	120	541	242 (44.7%)	182 (33.6%)	117 (21.6%)
Number of tablets	7	403	215 (53.4%)	108 (26.8%)	80 (19.8%)
	14	57	9 (15.8%)	32 (56.1%)	16 (28.1%)
	21	5	<3 (-)	3 (-)	0 (0%)
	28	509	138 (27.1%)	222 (43.6%)	149 (29.3%)
	≥30	304	18 (5.9%)	104 (34.2%)	182 (59.9%)

*A prescription redemption with a contemporaneous link to a dental procedure is defined as an etoricoxib prescription redeemed in the time frame of two weeks before to one week after a dental procedure. An etoricoxib prescription redemption without a contemporaneous link to a dental procedure is an etoricoxib prescription redemption occurring outside this time frame.

Among the prescription redemptions of etoricoxib with a contemporaneous link to a dental procedure, the prescribed dose was 120 mg for 63.4% of the prescription redemptions. Seven tablets were prescribed for 56.3% of the redeemed prescriptions with a contemporaneous link to a dental procedure, and only 4.7% of the redeemed prescriptions with a contemporaneous link to a dental procedure were for ≥30 tablets. (Table 10.2e)

Table 10.2e Distribution of etoricoxib prescription redemptions prescribed by a dentist during the period from 2012-2014 with a contemporaneous link to a dental procedure

		Prescription redemptions with a contemporaneous link to a dental procedure*
		N (% within strata)
Overall		382
Gender	Female	190 (49.7%)
	Male	192 (50.3%)
Age group at prescription redemption	16-25	41 (10.7%)
	26-35	81 (21.2%)
	36-45	61 (16.0%)
	46-55	69 (18.1%)
	56-65	80 (20.9%)
	66-75	41 (10.7%)
	>75	9 (2.4%)
Year at prescription redemption	2012	119 (31.2%)
	2013	114 (29.8%)
	2014	149 (39.0%)
Country	Denmark	6 (1.6%)
	Sweden	24 (6.3%)
	Finland	352 (92.2%)
Dose (mg/ tablet)	30	25 (6.5%)
	60	43 (11.3%)
	90	72 (18.9%)
	120	242 (63.4%)
Number of tablets	7	215 (56.3%)
	14	9 (2.4%)
	21	<3 (-)
	28	138 (36.1%)
	≥30	18 (4.7%)

* A prescription redemption with a contemporaneous link to a dental procedure is defined as an etoricoxib prescription redeemed in the time frame of two weeks before to one week after a dental procedure

One or more dental procedures were linked to 382 prescription redemptions. In total, there were 460 dental procedures. The most common dental procedures were: “Extraction of tooth” (31.7%), “Surgical removal of tooth” (33.9%), and “Dental cavity fillings without pulp communication” (10.2%). (Table 10.2f)

Table 10.2f. Distribution of dental procedures with a contemporaneous linkage* to etoricoxib prescription redemptions prescribed by a dentist during the period from 2012-2014

Type of dental procedure	Number and % of total dental procedures
Prescription redemptions, total	382
Procedures, total	460 (100%)
Dental cavity fillings without pulp communication	47 (10.2%)
Pulp capping	5 (1.1%)
Coronal amputation of pulp	<3 (-)
Opening to pulp and canal cleaning	35 (7.6%)
Surgical apical amputation	<3 (-)
Extraction of tooth	146 (31.7%)
Surgical removal of tooth	156 (33.9%)
Treatment of bleeding after extraction	0 (0%)
Periodontal treatment	32 (7.0%)
Expanded periodontal treatment	<3 (-)
Scaling of teeth**	0 (0%)
Scaling of root surfaces**	0 (0%)
Surgical periodontal treatment	0 (0%)
Surgical measures - implant treatment etc.	34 (7.4%)
Prosthetic measures	5 (1.1%)

*A prescription redemption with a contemporaneous link to a dental procedure is defined as an etoricoxib prescription redeemed in the time frame of two weeks before to one week after a dental procedure. An etoricoxib prescription redemption without a contemporaneous link to a dental procedure is an etoricoxib prescription redemption occurring outside this time frame.
**Often part of periodontal treatment

Table 10.2g shows the distribution of prescription redemptions without a contemporaneous link to a dental procedure and without a dental procedure during the study period stratified by gender, age, year, dose, and number of tablets dispensed.

Table 10.2g Distribution of etoricoxib prescription redemptions prescribed by a dentist during the period from 2012-2014 without a dental procedure or without a contemporaneous link to a dental procedure

		Prescription redemptions without a contemporaneous link to a dental procedure*	Prescription redemptions without a dental procedure
		N (% within strata)	N (% within strata)
Overall		469	427
Gender	Female	272 (58.0%)	262 (61.4%)
	Male	197 (42.0%)	165 (38.6%)
Age group at prescription redemption	0-15	<3 (-)	<3 (-)
	16-25	17 (3.6%)	63 (14.8%)
	26-35	53 (11.3%)	47 (11.0%)

		Prescription redemptions without a contemporaneous link to a dental procedure*	Prescription redemptions without a dental procedure
		N (% within strata)	N (% within strata)
	36-45	71 (15.1%)	66 (15.5%)
	46-55	115 (24.5%)	93 (21.8%)
	56-65	134 (28.6%)	116 (27.2%)
	66-75	51 (10.9%)	28 (6.6%)
	>75	28 (6.0%)	14 (3.3%)
Year at prescription redemption	2012	143 (30.5%)	133 (31.2%)
	2013	181 (38.6%)	169 (39.6%)
	2014	145 (30.9%)	125 (29.3%)
Country	Denmark	6 (1.3%)	0 (0%)
	Sweden	129 (27.5%)	206 (48.2%)
	Finland	334 (71.2%)	221 (51.8%)
Dose (mg/ tablet)	30	36 (7.7%)	42 (9.8%)
	60	121 (25.8%)	120 (28.1%)
	90	130 (27.7%)	148 (34.7%)
	120	182 (38.8%)	117 (27.4%)
Number of tablets	7	108 (23.0%)	80 (18.1%)
	14	32 (6.8%)	16 (3.8%)
	21	3 (0.6%)	0 (0%)
	28	222 (47.3%)	149 (34.9%)
	≥30	104 (22.2%)	182 (42.6%)

The off-label analysis focused on children ages <16 years and prescriptions of doses >90 mg.

There were <3 etoricoxib prescription redemptions with a recorded age <16 years. Due to the low number, no further analyses of these children were possible. (Table 10.2h)

A total of 42.3% of the prescription redemptions had a dose >90 mg (Table 10.2a). All of these prescriptions were for 120 mg tablets. Among men, 52.0% were prescribed doses >90 mg, while among women, only 34.9% were prescribed doses >90 mg. Among those 16-55 years old, 46-59% of the prescription redemptions were for doses >90 mg, while among those 56-75, 30-38% were for >90 mg tablets and only 11.8% of those >75 had prescription redemptions for >90 mg tablets. Only 10.0% of prescription redemptions in Sweden were for >90 mg tablets compared to 58.3 and 54.9% for Denmark and Finland, respectively. Ninety percent of prescription redemptions for 7 tablets were for >90 mg tablets, while only 18.1 and 11.5% of prescription redemptions for 28 and ≥30 tablets respectively were for >90 mg tablets. Of those prescription redemptions with a contemporaneous link to a dental procedure, two thirds were for >90 mg tablets; one third of prescription redemptions without a contemporaneous link to a dental procedure were for >90 mg tablets. Those prescription redemptions associated with tooth extractions and other surgical procedures such as implants were most likely to receive prescriptions for >90 mg tablets. (Table 10.2h)

Table 10.2h Distribution of use of etoricoxib >90 mg/tablet prescribed by a dentist with and without a procedure link

		Total number of prescriptions redeemed	Number of prescriptions redeemed with a dose > 90 mg/tablet N (% out of total prescription redemptions)
Overall		1278	541 (42.3%)
Gender	Female	724	253 (34.9%)
	Male	555	288 (52.0%)
Age group at prescription redemption	0-15	<3	<3 (-)
	16-25	121	57 (47.1%)
	26-35	181	106 (58.6%)
	36-45	198	101 (51.0%)
	46-55	277	128 (46.2%)
	56-65	330	98 (29.7%)
	66-75	120	45 (37.5%)
	>75	51	6 (11.8%)
Year at prescription redemption	2012	395	149 (37.7%)
	2013	464	149 (31.9%)
	2014	419	244 (58.2%)
Country	Denmark	12	7 (58.3%)
	Sweden	359	36 (10.0%)
	Finland	907	498 (54.9%)
Number of tablets	7	403	363 (90.1%)
	14	57	48 (84.2%)
	21	5	3 (60.0%)
	28	509	92 (18.1%)
	≥30	304	35 (11.5%)
Prescription redemptions with a contemporaneous link to a dental procedure*	Yes	382	242 (63.4%)
	No	896	299 (33.4%)

Type of procedures for prescription redemptions with a contemporaneous link to a dental procedure	Dental cavity fillings without pulp communication	17 (36.2%)
	Pulp capping	<3 (-)
	Coronal amputation of pulp	0 (0%)
	Opening to pulp and canal cleaning	12 (34.3%)
	Surgical apical amputation	<3 (-)
	Extraction of tooth	101 (69.7%)
	Surgical removal of tooth	126 (80.8%)
	Treatment of bleeding after extraction	0 (0%)
	Periodontal treatment	13 (40.6%)
	Expanded periodontal treatment	0 (0%)
	Scaling of teeth**	0 (0%)
	Scaling of root surfaces**	0 (0%)
	Surgical periodontal treatment	0 (0%)
	Surgical measures - implant treatment etc.	25 (73.5%)
	Prosthetic measures	<3 (-)

*A prescription redemption with a contemporaneous link to a dental procedure is defined as an etoricoxib prescription redeemed in the time frame of two weeks before to one week after a dental procedure. An

etoricoxib prescription redemption without a contemporaneous link to a dental procedure is an etoricoxib prescription redemption occurring outside this time frame
**Often part of periodontal treatment

Women were slightly less likely to have prescription redemptions for >90 mg tablets than men, and the youngest and oldest patients were less likely to be have prescription redemptions for >90 mg tablets. Two thirds of prescription redemptions for >90 mg tablets were for 7 tablets. (Table 10.2i)

Table 10.2i Distribution of use of etoricoxib >90 mg prescribed by a dentist stratified by gender, age, year, country, dose, and procedure link.

		Number of prescriptions redeemed with a dose > 90 mg/tablet N (%) within strata
Overall		541
Gender	Female	253 (46.8%)
	Male	288 (53.2%)
Age group at prescription redemption	16-25	57 (10.5%)
	26-35	106 (19.6%)
	36-45	101 (18.7%)
	46-55	128 (23.7%)
	56-65	98 (18.1%)
	66-75	45 (8.3%)
	>75	6 (1.1%)
Year at prescription redemption	2012	149 (27.5%)
	2013	149 (27.4%)
	2014	244 (45.1%)
Country	Denmark	7 (1.3%)
	Sweden	36 (6.7%)
	Finland	499 (92.0%)
Number of tablets	7	364 (67.1%)
	14	48 (8.9%)
	21	3 (0.6%)
	28	92 (17.0%)
	≥30	35 (6.5%)
Prescription redemptions with a contemporaneous link to a dental procedure*	Yes	242 (44.7%)
	No	299 (55.3%)

Information on the instructions for use given to the patients on the package sticker regarding how long to take etoricoxib is not available in the prescription registers. The distribution of the number of redeemed tablets is provided in Tables 10.1a/b, 10.2a/b/c and 10.2c. In many cases, the number of tablets dispensed reflects the minimum package size available in the country.

No data were provided in Finland regarding anti-coagulants. No individuals in Denmark had an overlap between an etoricoxib and an anti-coagulant prescription. Less than 22 etoricoxib

prescription redemptions in Sweden had an overlapping prescription for an anti-coagulant and of these, 16 individuals had an anti-coagulant redemption less than 30 days before redemption of etoricoxib. (Table 10.2j)

Table 10.2j. Distribution of individuals with overlapping prescription redemptions of etoricoxib prescribed by a dentist and prescription redemptions of anti-coagulants.

		Individuals redeeming a prescription of anticoagulant before an etoricoxib prescription redemption N*
Time period between anticoagulants and etoricoxib prescription redemption	0-14 days	9
	15-29 days	7
	30-59 days	<3
	60-90 days	3

***** Individuals will only be included once. If an individual is eligible for more than one time period category, the individual will only be included in the time period where the interval between the etoricoxib and the anti-coagulant prescription redemptions is the shortest.

10.3 Outcomes

Not applicable.

10.4 Main results

See sections 10.1 and 10.2 above.

10.5 Other analyses

A “contemporaneous linkage" between an etoricoxib prescription redemption and a dental procedure was defined as an etoricoxib prescription redeemed in the time frame of two weeks before to one week after a dental procedure. The effect of the selected time frame for the definition of a contemporaneous linkage between an etoricoxib prescription redemption and a dental procedure was evaluated in a sensitivity analysis that modified the time frame to four weeks before to two weeks after a dental procedure. The modified time frame resulted in only a few additional prescription redemptions with a contemporaneous link. The number of prescription redemptions with a contemporaneous link to a dental procedure changed from 382 (29.9%) to 405 (31.7%) (data not shown in tables).

10.6 Adverse events/adverse reactions

Not applicable.

11 DISCUSSION

11.1 Key results

National dental experts were consulted to comment on some of the findings in the study. Their comments are incorporated in the discussion of results below.

The overall utilization of etoricoxib for dental pain was quite low. Over the 3 year period from 2012-2014, there were a total of 1615 redemptions of prescriptions for etoricoxib written by dentists in Denmark, Sweden, Finland and Norway. The largest number of prescriptions was in Finland. There were only 12 prescriptions for etoricoxib written by dentists redeemed in Denmark over the 3 year period. The Danish expert states that there has been a major debate in Denmark concerning the use of selective COX-2 inhibitors and Danish guidelines recommend using other drugs rather than etoricoxib.

Unexpectedly, only 30% of the prescription redemptions had a contemporaneous link to a dental procedure. A prescription was considered contemporaneously linked to a dental procedure if it was redeemed in the time frame of two weeks before to one week after a procedure. An additional 37% of redeemed prescriptions were to individuals with a dental procedure outside of that time frame. One third of the prescription redemptions had no registered dental procedure during the study period. One possible explanation is that dentists may be prescribing etoricoxib for dental pain not associated with a specific procedure. The Finnish dental expert states that in Finland, etoricoxib is perceived as an effective pain reliever so it may be prescribed without a prior dental procedure if a patient experiences high levels of dental pain; however, this is not perceived as standard practice. The expert also indicated that etoricoxib has been used successfully for temporomandibular joint pain conditions and especially in cases of osteoarthritis (although it would be expected that prescriptions for the latter would be written by physicians rather than dentists).

There were <3 etoricoxib prescription redemptions with a recorded age <16 years over the 3 year study period. Thus off-label use in this population appears to be limited.

A total of 42.3% of the prescription redemptions were for >90 mg tablets in Denmark, Finland and Sweden. A total of 57.9% of the prescription redemptions were for >90 mg tablets in Norway. National experts have not been able to provide an explanation for the relatively high proportion of prescription redemptions for >90 mg tablets. They noted that national guidelines are consistent with the etoricoxib label and recommend a dose of 90 mg once daily for up to three days. It is possible that individual dentists have found higher doses to be more effective or that the higher doses are being used for dental conditions associated with high levels of pain such as temporomandibular joint pain, dental abscesses, implants, or periodontal procedures.

Nearly all (98%) of the dental prescriptions redeemed in Norway were for 28 tablets or less, and three quarters of the redeemed prescriptions were for 28 tablets or less in Denmark, Sweden, and Finland. Given that the minimum package sizes in the Nordic countries range from 2 to 28 tablets and the fact that information on the instructions for use given to the patients on the package sticker in terms of number of days to take etoricoxib are not available

from the prescription registers, it is difficult to ascertain how much off label use for >3 days actually occurs. The experts consulted in the study did not report any other mechanisms than the pharmaceutical leaflets discouraging use for >3 days. In addition, given that dentists appear to be prescribing etoricoxib for dental pain conditions not associated with a procedure, they may instruct patients to take etoricoxib for more than 3 days. No explanation for why package sizes of 30 tablets or more were prescribed is available. It is possible that a larger number of tablets might be prescribed when it is anticipated that a patient will have additional procedures (e.g., patients who are having dental implants may have several procedures over multiple months).

Only 16 patients in Sweden had an anti-coagulant prescription redemption within 30 days prior to a prescription redemption of etoricoxib; 9 of which were within 14 days. No information was available in the prescription database regarding whether patients were told to hold their anticoagulant prescriptions while taking etoricoxib. The small number of patients with overlapping prescriptions, suggests that drug-drug interactions between etoricoxib and anti-coagulants while posing a possible risk, do not appear to be a significant concern on a population basis.

11.2 Limitations

The register data used in this study did not include direct information on the reason for etoricoxib prescribing. Consequently, the relationship between prescriptions and procedures within a particular time window had to be inferred. Because of the data request process for the registers, the procedures of interest had to be prespecified. It is possible that some relevant procedures were not included in the prespecified list. In addition, no information on dental diagnoses (rather than procedures) associated with the prescriptions was collected.

The unit of analysis for this study was etoricoxib prescription redemptions, not individual patients. The total number of patients included and how many patients had more than one etoricoxib prescription redemption from 2012-2014 are not known. It is likely that there would be some patients with more than one prescription redemption.

Data on dental procedures performed in individuals who redeemed an etoricoxib prescription in Norway were not available due to restrictions on data access. Therefore, all analyses have been performed for Denmark, Finland and Sweden without including data from Norway. Data from Norway regarding etoricoxib prescriptions were analysed and presented separately.

No information on instructions for use provided on the package sticker was available from the prescription registers to provide insight into the duration of use. There also was no information on the instructions for use in terms of the treatment regimen and recommended total daily dose.

Prescription redemptions of anti-coagulants in Finland and Norway were not available for the study. The analysis of potential drug interaction between etoricoxib and anti-coagulants (i.e., patients who are prescribed etoricoxib who also have concurrent prescriptions for anti-coagulants) was limited to Denmark and Sweden.

11.3 Interpretation

See conclusion in Section 13 below.

The MAH conducted an internal survey of spontaneous and non-interventional postmarketing reports from health care providers and consumers of etoricoxib use for dental indications received globally between 2012 and 2017. These reports were evaluated for adverse events (AEs) associated with, and narrative descriptions of, off label use including off label paediatric use and overdose. Reports that described off label use of etoricoxib for dental use outside the core company data sheet labeled indication (treatment of moderate to severe acute post-operative pain associated with dental surgery) and dosage information were assessed for additional AEs to determine whether a higher than expected proportion of serious adverse events (SAEs) was reported and whether an unexpected pattern of AEs was reported. The survey results revealed a low number of reports of off label use for dental indications during the interval with a lower than expected proportion of SAEs and a pattern of AE generally consistent with the known safety profile of etoricoxib. There were no reports of off label paediatric use.

11.4 Generalisability

Overall prescribing rates of etoricoxib by dentists in Europe appear to be quite low. Given the heterogeneity in etoricoxib prescribing by dentists across the 4 countries in this study, the generalisibility of these results is unknown. At the time this study was started, these were the only countries for which data on etoricoxib prescribing by dentists and dental procedure data were available.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

The overall utilization of etoricoxib for dental pain across Denmark, Sweden, Finland, and Norway from 2012-2014 was quite low. Over the 3 year period, there were a total of 1615 redemptions of etoricoxib prescriptions written by dentists in the 4 countries. The prescription pattern varied across countries. While some dentists appear to be prescribing etoricoxib for conditions other than dental pain associated with procedures, at higher than recommended doses, and potentially for longer than 3 days, given the low overall prescribing rate by dentists, it is unlikely that this infrequent off-label use with dental procedures in the Nordic countries would be of significant public health concern.on a population basis. Use in patients <16 years of age or in patients with overlapping prescriptions for anti-coagulants appear to be very infrequent.

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ANNEX 1 LIST OF STAND ALONE DOCUMENTS

Not applicable.

ANNEX 2 STUDY PROTOCOL

(03YSY4)

Merck No.: MK-0663-170-00
Epidemiology No.: 07013.025.14.082 1
EU PAS Register No./ EUDRACT No.: TBD

PASS information

Title	A non-interventional, population-based register study on the prescription of etoricoxib (Arcoxia®) to dental surgery patients in the Nordic countries
Protocol version identifier	Final 1.0
Date of last version of protocol	7 October 2013
EU PAS register number	TBD
Active substance	Etoricoxib ATC Code: M01AH05
Medicinal product	Etoricoxib (Arcoxia)
Product reference	UK/H/0532/01-04
Procedure number	TBD
Marketing authorisation holder(s)	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
Joint PASS	No

Research question and objectives	Characterize dispensed etoricoxib prescribed by dentists including off-label use.
	The specific objectives are:
	• To describe dispensed etoricoxib prescribed by dentists including the associated dental procedures, patient demographics (age, gender), dosing, year, and country
	• To describe any dispensed etoricoxib prescribed by dentists not associated with dental procedures
	• To describe off-label use by dentists in patients
	  ○ less than 16 years of age
	  ○ with doses >90mg/day
	including the associated dental procedures, patient demographics (age, gender), dosing, year, and country
	• To describe the duration of use / number of tablets dispensed

Country(-ies) of study	Denmark, Finland, Norway, and Sweden
Author	PPD National Institute of Public Health, University of Southern Denmark, Øster Farimagsgade 5A, 1353 Copenhagen, Denmark PPD

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
MAH contact person	PPD

1. Table of contents

2. List of abbreviations

ApEHR	Institute of Applied Economics and Health Research
CPR	Unique personal identification number (CPR number)
EMA	European Medicines Agency
EU	The European Union
FDA	US Food and Drug Administration
MHRA	Medicines and Healthcare products Regulatory Agency
NIPH	National Institute of Public Health, University of Southern Denmark
REK	Regional Ethics Committee, Norway
THL	National Institute for Health and Welfare, Finland

3. Responsible parties

Institute of Applied Economics and Health Research

- PPD
- PPD Odense University Hospital and University of Southern Denmark

National Institute of Public Health, University of Southern Denmark

- PPD
- PPD

National scientific coordinators

- Denmark: PPD National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark
- Finland: PPD School of Public Health, University of Tampere, Finland
- Norway: PPD University of Oslo, Norway and PPD Institute of Public Health, University of Southern Denmark at Odense
- Sweden: PPD University of Gothenburg and Centre for Health Economics at the University of Gothenburg, Sweden.

Expert group

- Experts will be included as the project starts

4. Abstract

Title: A non-interventional, population-based register study on the prescription of etoricoxib (Arcoxia®) to dental surgery patients in the Nordic countries.

Rationale and background

Treatment of pain associated with dental surgery is a new indication for etoricoxib (i.e, initiated in 2012). Potential risks include off-label use of etoricoxib in patients less than 16 years of age or with doses >90 mg/day or for more than 3 days. Following a request by the European Medicines and Healthcare products Regulatory Agency (MHRA), a study should be performed for the assessment of the safety of etoricoxib when prescribed in a dental surgery setting.

Research question and objectives

Characterize dispensed etoricoxib prescribed by dentists including off-label use.
The specific objectives are:

- To describe dispensed etoricoxib prescribed by dentists including the associated dental procedures, patient demographics (age, gender), dosing, year, and country
- To describe any dispensed etoricoxib prescribed by dentists not associated with dental procedures
- To describe off-label use by dentists in patients
    - less than 16 years of age
    - with doses >90mg/day

  including the associated dental procedures, patient demographics (age, gender), dosing, year, and country.
- To describe, where possible, the duration of dental prescriptions, number of tablets dispensed / package size, as well as mechanisms in place in each country, such as stickers with instructions for use to discourage use for >3 days
- To describe patients who are prescribed etoricoxib who also have concurrent prescriptions for anti-coagulants (with the caveat that patients may have been told to hold their anti-coagulants for a few days around the dental procedure) to monitor the potential for drug interaction

Study design

A longitudinal nation-wide register-based study on etoricoxib prescriptions in dental practices including all individuals who purchased an etoricoxib prescription prescribed by dentists.

Population

The population comprises all individuals in the four Nordic countries in the period 2012-2013 with dispensed etoricoxib prescribed by dentists.

Variables

Etoricoxib prescription (date, dose, tablets, etc.), dental procedures (type and date), and patient demographics (age and gender).

Data sources

Nation-wide registers with information on prescription drugs and dental procedures. The following national registers will be used: prescription registers, health services registers, and civil registration systems.

Study size

No hypothesis will be tested. Therefore, no sample size or power calculation is performed.

Data analysis

Descriptive analyses will be performed characterizing the dispensed etoricoxib prescribed by dentists by means of frequency distributions of etoricoxib dispensed and dose, stratified by dental procedures, patient demographics (age, gender), year, and country. Off-label use will be characterized by prescriptions in patients less than 16 years and doses >90 mg/day. Descriptive data will be provided on duration of use / number of tablets dispensed where possible.

5. Amendments and updates

Updates have been made since the original submission of the protocol concept to provide more information on the study. In addition, the protocol has been updated to address concerns raised by the MHRA (Reference Member State) and Concerned Member States.

6. Milestones

Table 1. Time schedule and Milestones

Milestone	Planned date
Start of data collection	01Jul2014
End of data collection	24Nov2014
Interim report 1	Not applicable
Registration in the EU PAS register	TBD
Final report of study results	30Sep2015

The time schedule of the study will depend on the approval process in the different countries. The proposed time schedule is based on an estimate of the time required for the approval process by the authorities. The responsible parties do not have any possibility to influence the administrative procedures and the requirements that the national authorities or owners of registers impose on studies. If there are any significant delays in getting approvals / accessing data in any of the countries, the MAH will inform MHRA.

7. Rationale and background

Etoricoxib is a selective COX-2 inhibitor belonging to the non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are commonly prescribed in dental practice for the management of pain and swelling [Roda et al 2007]. Etoricoxib was originally approved in 2003. It is marketed under several trade names such as Arcoxia, Algix, Tanxib, Nocoxia, and Etorix. Etoricoxib is indicated for the symptomatic relief of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, the pain and signs of inflammation associated with acute gouty arthritis, and as of 2012, for short-term treatment of moderate pain associated with dental surgery. For the treatment of moderate pain associated with dental surgery, "the recommended dose is 90 mg once daily, limited to a maximum of 3 days" [http://www.medicines.org.uk/emc/medicine/8734#POSOLOGY]. Labeling also indicates "some patients may require additional postoperative analgesia" (i.e., rescue therapy during etoricoxib treatment). Etoricoxib is contraindicated in "Children and adolescents under 16 years of age" [http://www.medicines.org.uk/emc/medicine/8734#CONTRAINDICATIONS].

Etoricoxib is available as 30, 60, 90, and 120 mg tablets. The Anatomical Therapeutic Classification (ATC) code is M01AH05.

Treatment of pain associated with dental surgery is a new indication for etoricoxib (2012). Potential risks include off-label use of etoricoxib in patients less than 16 years of age. Following a request by the European Medicines and Healthcare products Regulatory Agency (MHRA), a study should be performed to characterize off-label use in the dental surgery setting, including paediatric use.

To assess the use of etoricoxib, detailed information on prescriptions for post-operative dental pain will be obtained from the national registers in Denmark, Finland, Norway, and Sweden on an individual basis. The dental surgery procedure(s) that are carried out on the patient, which are associated with the prescription of etoricoxib for post-operative pain will also be obtained, as applicable. Finally, in order to record possible prescribing to people under the age of 16, the age and gender of the patients receiving etoricoxib will be analyzed. Due to general reimbursement of dispensed NSAIDs and the majority of necessary health care procedures, data on dispensed dental prescriptions of etoricoxib, and most dental procedures are available in all four countries.

Very little is known about the use of etoricoxib among dentists, and no specific data is available about the use in Nordic countries. A reasonable estimate is less than 500 prescriptions per year for the Nordic countries. There is currently no published information on dental use of etoricoxib and dental off-label use. Consequently, a total population study is necessary in order to evaluate use of etoricoxib and specifically if there is off-label use of etoricoxib by dentists. Dental prescription of etoricoxib may be considered off-label in people under 16 years of age or if doses > 90 mg/day are prescribed. Duration of treatment cannot be assessed because the instructions to the patient about duration of use are not consistently available across the Nordic region, and the packaging of etoricoxib may include supplies for more than 3 days treatment. The minimum package sizes in the Nordic countries are 2, 5, 7, and 28 tablets in Denmark, Finland, Norway, and Sweden, respectively.

The Nordic health and prescription registers contain information needed to perform an analysis to meet the above objectives. In 2011, approximately 3 million total dispensed prescriptions for NSAIDS were issued in the Nordic countries combined. In Finland, in 2011 a total of 300,000 dispensed prescriptions of COX-2

inhibitors were issued. Each of the 5150 dentists in Finland write on average about 87 prescriptions per year. Approximately 100,000 of these dispensed prescriptions were for NSAIDs [http://www.medicines.org.uk/emc/medicine/8734#CONTRAINDICATIONS, www.medstat.dk, http://www.norpd.no/, http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel, http://www.kela.fi/web/en/statistical-database-kelasto].

Data from the Danish National Prescription Register [www.medstat.dk] indicate that about 8,778 and 13,071 Danish citizens dispensed prescriptions for etoricoxib by a prescription at least once annually in 2003 and 2004, respectively. The number of Danish citizens who dispensed prescriptions for etoricoxib at least once annually decreased to 1,663 and 1,284 individuals in 2011 and 2012, respectively. The annual number of Danish children (age 0-14 years) who dispensed a prescription for etoricoxib at least once annually ranged from 0-8 children in 2003-2012, in 2011-2012, no children (0-14 years) were prescribed etoricoxib.

Off-label usage of NSAIDs has been analyzed in several studies, especially among neonates and infants in hospital wards. From Table 2 the frequency of off-label usage in children in Swedish hospitals is described. In total, 41% of all authorized drugs were given off-label and the highest proportion of off-label prescriptions occurred in neonates and infants in intensive care [Kimland et al 2012]. Off-label drug prescriptions in hospitals vary considerably among ATC-groups. According to Table 2 the largest number of off-label drug prescriptions is found among drugs for the nervous system (N), analgesics (mostly paracetamol), blood and blood-forming organs (B), and the alimentary tract and metabolism (A). The highest proportion of off-label classification was found among drugs for the eye (S), for the skin (D), and drugs for blood or blood-forming organs (B). The NSAID diclofenac was prescribed in 2.1% of the off-label pediatric cases.

Table 2 The most commonly prescribed approved drugs used off-label in hospitalized Swedish children (Sweden 2011) [Kimland et al 2012**]**

3879 off-label prescriptions in 2947 children of totally 11,294 prescriptions= 34%		(n=3879)	
Substances	ATC	Number	%
Carbohydrates	B	479	12.3
Electrolytes +/- carbohydrates	B	341	8.8
Paracetamole	N	320	8.2
Sodium chloride	B	113	2.9
Epinephrine	C	103	2.7
Morphine	N	102	2.6
Midazolam	N	87	2.2
Sulfamethoxazole/ trimethoprim	J	84	2.2
Diclofenac	M	83	2.1
Heparin	B	81	2.1

8. Research question and objectives

Characterize dispensed etoricoxib prescribed by dentists including off-label use.

The specific objectives are:

- To describe dispensed etoricoxib prescribed by dentists including the associated dental procedures, patient demographics (age, gender), dosing, year, and country
- To describe any dispensed etoricoxib prescribed by dentists not associated with dental procedures
- To describe off-label use by dentists in patients
    - less than 16 years of age
    - with doses >90mg/day

  including the associated dental procedures, patient demographics (age, gender), dosing, year, and country
- To describe, where possible, the duration of dental prescriptions, number of tablets dispensed / package size, as well as mechanisms in place in each country such as stickers with instructions for use to discourage use for >3 days
- To describe patients who are prescribed etoricoxib who also have concurrent prescription for anti-coagulants (with the caveat that patients may have been told to hold their anti-coagulants for a few days around the dental procedure) to monitor the potential for drug interaction

The study is a descriptive analysis of the use of etoricoxib prescribed by dentists. No hypothesis will be tested.

9. Research methods

9.1. Study design

A non-interventional, population-based study of dispensed etoricoxib prescriptions in dental practice in the Nordic countries will be performed using prescription register data.

A longitudinal study design will be used including all individuals who receive a dispensed etoricoxib prescription prescribed by dentists in the period 2012-2013. In order to ensure adequate data to address the off-label use questions, the national registers from all four Nordic countries will be used for study.

No hypothesis is tested and therefore, no sample size calculation has been performed.

Data on dispensed etoricoxib prescriptions by dentists will be made available from the national prescription drug registers in all four countries. The dispensed dental prescriptions will be linked with data on performed dental procedures on an individual level, based on reimbursement data from national health

services registers. The use of etoricoxib for dental surgery in hospital wards is minimal, but inpatient procedures will be included.

For completeness, if dispensed prescriptions of etoricoxib not associated with a dental surgery procedure are identified in the registers, these prescriptions will still be noted and analyzed. The claim may not have been posted by the dentist or the prescription may have been used for non-surgical dental pain (e.g., in the context of an infection (dental abscess) being treated medically with antibiotics and analgesia).

9.2. Setting

The study population consists of all individuals who purchased etoricoxib prescribed by dentists. Because the dental pain indication for etoricoxib was approved for use in the EU in 2012, the study period is 2012-2013 for all four countries. The national prescription and health services registers in the Nordic countries enable this study to cover the whole population of individuals with an etoricoxib prescription by dentists and ensures valid estimates for the Nordic countries.

The study will cover all prescriptions of etoricoxib purchased at a pharmacy (dispensed and paid for) and prescribed by dentists, since these are the only prescriptions tracked in the national prescription registers. Etoricoxib that is handed directly to the patients in hospital wards or by the dentists will not be included. Prescriptions that have not been used, because the patient, for whatever reason, decides not to collect the drugs in the pharmacy, are not included in this study. Etoricoxib is not available over the counter (OTC).

9.3. Variables

The pattern of prescribed etoricoxib will be characterized using frequency distributions stratified by dental procedures, dosing, patient demographics (age, gender), year, and country (Table 3). Prescription medicine is identified in all Nordic countries by ATC code.

Information about the timing of etoricoxib prescribing relative to procedures, and the strength of preparation (dosage), package size and number of packages of etoricoxib supplied will be analyzed.

Dental etoricoxib prescriptions, which are prescribed in connection to one or more defined dental procedures within a specific time frame, will be identified using a time window of two weeks before a dental procedure and up to one week after a dental procedure. Etoricoxib dispensed which do not occur within the relevant time window of a dental procedure will be analyzed separately.

Table 3 Variables included in the study

Type of variable	Description of variable	Data source (see also table 3)
Outcome variable	Etoricoxib dispensed (ATC code: M01AH05), including date of purchase, package size (number of tablets), number of packages, dose strength (mg), prescriber, and dosing instructions if available	National prescription registers
Stratification variables	Age ((child (<16 years), adult (≥16 years)), 5-year age groups (if adequate data are available)) Gender (male, female) Year (2012, 2013), if adequate data are available Country (Denmark, Finland, Norway, and Sweden)	Civil registration systems
	Indication of prescription (dental procedure), date, and dentist identification number. If no procedure is available for a prescription, the procedure will be coded as "Etoricoxib prescription without a clear procedure link"	National health services registers National patient registers
Concomitant medication	Prescriptions for anti-coagulants (Factor Xa inhibitors, oral thrombin inhibitors, and prescription aspirin), date	National prescription registers
Other variables	Mortality (date), Migration (dates of immigration, dates of emigration)	Civil registration systems

9.4. Data sources

The study population comprises individualsin Denmark, Finland, Norway, and Sweden with dispensed etoricoxib prescribed by dentists and purchased in 2012 and 2013.

Exceptional opportunities to perform register-based research are driven by the unique personal identification number (CPR number) introduced in the Nordic countries in the 1960's and available to all persons with permanent residence in the Nordic countries (Pedersen, 2011). The CPR number makes it possible to link information at the individual level from several registers for scientific research purposes (Gissler 2004, Thygesen 2011). The national prescription and national health services registers within each of the Nordic countries capture all the individual encounters of purchasing etoricoxib prescribed by dentists and its indications.

We utilize the nation-wide registers of prescription, health services (contact to dentists) and the civil registration system. The registers cover different periods (Table 4), but all registers have information for the period 2012-2013. The data from the different registers for the year 2013 is expected to be available between February and September 2014 (see table 4).

Table 4 National health registers in the Nordic countries of relevance for the present study including registration period

Register	Country			
	Denmark	**Finland**	**Norway**	**Sweden**
National prescription register	1995-2013	1994-2013	2004-2013	2005-2013
National health service register	1990-2013	2011-2013	2006-2013	2001-2013
National patient register	1977-2013	1967-2013	2008-2013	1987-2013
Civil registration system	1968-2013	1967-2013	1964-2013	1965-2013
Study period	2012-2013	2012-2013	2012-2013	2012-2013
Availability of data for 2013 in registers	March to May 2014	Feb to Sept 2014	March to June 2014	March to June 2014

The dental procedures will be extracted from the national health services registers. The procedure codes vary between the Nordic countries. A list of procedure codes is listed in Table 5. The specific codes to be used will be identified in conjunction with dentists in each country familiar with the relevant coding systems.

Table 5 **Dental surgery procedures and national dental reimbursement codes**

	Dental procedure codes			
	Denmark	**Sweden**	**Norway**	**Finland**
Dental cavity fillings without pulp communication	1501-1559	701-708, 321-322	201-207,	SCE00, SFA 00,10,30,40
Pulp capping	1600	521		SGB00
Coronal amputation of pulp	1601			SGC10
Opening to pulp and canal cleaning	1605	501-504, 522	210-212	SGA01-07
Surgical apical amputation	1606	541	406-409	SGC50
Extraction of tooth	1701	401-403	401-402	EBA00, EBA05
Surgical removal of tooth	1801	404-406	403-405	EBA10,12, 20,30,40,45
Treatment of bleeding after extraction	1705	480		
Periodontal treatment	1420	341	501	SDA01-02
Expanded periodontal treatment	1430	342-343	503-505	SDA03-05
Scaling of teeth*	1425			
Scaling of root surfaces*	1431			
Surgical periodontal treatment	1440	442-445	502,514, 516-517,	SDA10-11
Surgical measures - implant treatment etc.	420-430, 435-436		412-423, 410-420	
Prosthetic measures		801-809, 811-815, 822-829, 831-839 852-857, 861-865, 871-878,	301-315	

* Often part of periodontal treatment

9.5. Study size

The background population is the whole population in the Nordic countries, in total around 22 million people.

From this population, all individuals who purchased a prescription for etoricoxib prescribed by dentists in 2012-2013 will be evaluated.

A survey from year 2001 indicates that at least three in ten people receive one or more prescriptions for NSAIDs per year. The frequency and indications for dental prescriptions of etoricoxib in the Nordic countries is not known.

Because all etoricoxib prescriptions by dentists will be extracted and linked to procedures and demographic information, the study can describe off-label use that occurs (doses >90 mg and use in patients <16 years of age). The study will also describe duration of use, where available, or the number of tablets dispensed / package size. In general, instructions for use are not available in the registers. We will also describe mechanisms in place in each country (e.g., stickers with instructions for use) to discourage use for >3 days.

This study is purely descriptive and no hypothesis testing will be done. Therefore, no sample size / power calculations are necessary.

9.6. Data management

The handling of data in the etoricoxib study involves six steps and requires submissions of applications and approvals for access to data in the four Nordic countries. In addition to the acquisition and management of data, the primary scientific coordinator from Denmark will be responsible for the overall study and establishment of a joint Nordic data set. The Finnish, Norwegian, and Swedish national scientific coordinators will be responsible for steps 1-4 in each country, and the primary scientific coordinator will be responsible for steps 1-4 for Denmark and 5-6 for all countries.

The handling of data is planned to fall into the following six steps:

1. All national scientific coordinators will submit applications to the relevant authorities and agencies for permission to perform the study and to get access to data, including Statistics Denmark/Statistics Finland/Statistics Norway/Statistics Sweden and relevant health authorities to search the national prescription registers for all dispensed etoricoxib prescribed by dentists.
2. Each national scientific coordinator will facilitate the construction of the national study populations, consisting of:
    - all etoricoxib users (i.e. prescription purchasers) and prescriptions during the study period 2012-2013 prescribed by dentists
    - the associated dental procedures performed either on an outpatient or inpatient basis
    - patient demographics.

    Each national scientific coordinator is responsible for acquiring and validating the data sets.

    Data extraction for each country will be done as described below:

    All etoricoxib users will be extracted from the national prescription registers for 2012-2013. The dental procedures and patient demographics for the etoricoxib users (identified CPR numbers) will be extracted from the health service registers, the national patient registers, and the civil registration systems. Data will be merged by an anonymized CPR number. All national scientific coordinators will take responsibility for how the datasets can be combined within the four registers (See details in section 9.4) according to the specific regulatory and administrative procedures applicable in each of the four countries.

Quality control of data includes - but is not restricted to - check for legal values for each categorical variable, check for consistency between dates (e.g. date of birth before all other dates), and check and advise on the handling of missing data. Each national scientific coordinator will produce a document describing the checks performed and describing how the final dataset should be constructed from the individual country data including reasons for modifications and exclusions. For this process, all national coordinators will need to agree on the potential reasons for exclusion, e.g. missing value on crucial variables, chronological errors in the relation between dates, non-legal values of categorical variables, and extreme values of continuous variables. In case a dentist prescribes etoricoxib and no dental procedure can be identified to justify the prescription the prescription will be coded as "Etoricoxib prescription without a clear procedure link".

3. The datasets from Finland, Norway, and Sweden will be transferred to Statistics Denmark where all subsequent data handling will be done by the Danish scientific coordinator / primary study coordinator.
4. The primary study coordinator will link the data as described by the document developed by all national scientific coordinators and the data sets from all countries will be merged into a combined analysis data set.
5. The primary study coordinator will assess the data validity of the merged data set from all countries by logic checks and examination of extreme values and missing data. It is important that identification numbers (CPR numbers anonymised in a unique manner) are maintained to facilitate linkage back to the original data sets to be able to check the data and for the sake of transparency.

The data management steps 1-4 for Denmark and 5-6 will be performed on servers of Statistics Denmark. The programming will be performed by two independent researchers ensuring a high quality. The statistical programs will be stored at the servers on Statistics Denmark.

9.7. Data analysis

The statistical analyses will be performed using SAS version 9.3, R, and/or STATA version 12.

Only descriptive statistics will be performed, as no hypothesis will be tested.

In order to characterize the etoricoxib use prescribed by dentists the following descriptive analyses will be performed for the Nordic countries:

1. Distribution of dental procedures in patients with etoricoxib prescribed by a dentist overall and stratified by patient demographics (age (<16, ≥16 and 5-year age groups), gender), year, and country. Stratification for some variables may not be possible if data are very limited.
2. Distribution of the etoricoxib prescriptions overall and stratified by dose, patient demographics (age (<16, ≥16 and 5-year age groups), gender), year, and country. Stratification for some variables may not be possible if data are very limited.
3. Distribution of dental etoricoxib prescriptions, which are prescribed in connection to one or more defined dental procedures within a specific time frame from two weeks before a dental procedure and up to one week after a dental procedure. Etoricoxib prescriptions which do not occur within the relevant time window of a dental procedure will be coded as "Etoricoxib prescription without a

clear procedure link". The distribution of the etoricoxib prescriptions connected with a dental procedure versus prescriptions without a clear procedure link will be tabulated by specific dental procedure if present, dose, patient demographics (age (<16, ≥16 and 5-year age groups), gender), year, and country.

4. Distribution of off-label use:
    a. Any use of etoricoxib in individuals under 16 years of age characterized by dose, dental procedure (present, absent), specific dental procedure, patient demographics (age, gender), year, and country.
    b. Any use of etoricoxib >90mg/day will be characterized by dose, dental procedure (present, absent), specific dental procedure, patient demographics (age (<16, ≥16 and 5-year age groups), gender), year, and country. If dosing instructions are available, a qualitative assessment of more than 3 days use will be performed. Given that limited data on dosing instructions are expected to be available, package size will be described to characterize the potential for off-label use.
5. Description of number of patients with concurrent (overlapping) prescriptions for anti-coagulants (e.g. Factor Xa, oral thrombin inhibitors, and prescription aspirin) to monitor the potential for drug interactions (with the caveat that patients may have been told to hold their anti-coagulants for a few days around the dental procedure)

9.8. Quality control

Previous studies have evaluated the validity of the central registers, e.g. the prescription registers and the national health services registers (Kildemoes et al 2011, Andersen et al 2011, Klaukka 2001). These studies in general support that the validity and completeness of the data sources are high and satisfactory.

The descriptive analyses will be performed on the servers of Statistics Denmark. The programming will be performed by two experienced researchers independently in order to ensure high quality and limit the number of errors. Data and the statistical programs will be stored at the servers at Statistics Denmark.

9.9. Limitations of the research methods

1. The main limitation is that due to data availability, the study is limited to Denmark, Sweden, Norway, and Finland. The MAH and Academic Research Organization made a concerted effort to identify other countries where data on dental prescriptions, procedures, and demographics were available and could be linked, but were unable to identify any additional EU member states with such data sources.
2. Use of etoricoxib for dental pain across the EU is limited. While it is approved in the EU, there are some countries (e.g., the UK) where it is not listed on the dental formulary, and in other countries, because the MAH does not promote it / provide information to dentists, the number of prescriptions is very low. We have very little information on how many dental prescriptions have been written in the Nordic countries in 2012-2013 so it may turn out that the ability to characterize dental use is limited.
3. The prescription registers only contain information on dispensed medications, and no information on the actual consumption of drugs.
4. If prescriptions are collected several days before surgery procedure it cannot be determined whether the use of the drug started before the procedure. Some dentists will prescribe NSAIDs prior to a dental

procedure for prophylactic analgesia. Most dentists will write the prescription after surgery, and ask the patient to start taking the drug before the anesthetic effect disappears.

5. Prescriptions dispensed directly to the patients in the hospital or dental clinic will not be analyzed in this study.
6. Etoricoxib is supplied in blister packs so the minimum number of tablets prescribed may be limited by the smallest size of the blister pack (see Section 7). The number of tablets prescribed will not necessarily correspond to the instructions for duration of use provided to the patient. Therefore, if duration of treatment is not available from the prescription data, it will not be possible to determine if use of etoricoxib for >3 days occurs. The study will describe dispensed package size, the potential for off-label use, and the mechanisms in place in each country (e.g., stickers with instructions for use) to discourage use for >3 days.
7. Low dose aspirin is sold over the counter in the Nordic regions so the potential for an interaction with etoricoxib cannot be assessed. Information on whether patients have been told to stop their anti-coagulants for a few days around the dental procedure will not be available from the registers.
8. Hidden off-label usage of etoricoxib in children, where the prescription is made to a parent is not likely (nor legal), as all children currently have their own CPR numbers in all the Nordic countries. Furthermore, all Health Care Professionals (HCPs) are obliged to prescribe to the specific patient in order to ensure correct dosage and database registration. If a prescription is written to a person other than the specific patient, it is unlikely that a relation between the prescription and the procedure on the actual patient can be made. Such relationship can only be established by direct contact to the dentist in question, which is beyond the scope of this study. Such a prescription will most likely be defined as “Etoricoxib prescription without a clear procedure link”.

10. Protection of human subjects

This is an observational study with no administration of any therapeutic or prophylactic agent. Patients observed in this study will continue with the normal standard of care as provided by their personal physician. National registers of prescriptions and health services will be the sole data source.

11. Management and reporting of adverse events/adverse reactions

Definition of Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or who undergoes a protocol-specified procedure and which does not necessarily have to have a causal relationship with this treatment or procedure. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal l product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor’s product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during the course of the use of the Sponsor's product in studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Definition of Serious Adverse Event

"Serious Adverse Event" (SAE) means an adverse event which is fatal or life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly/birth defect, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Other Relevant Safety Information

The following events are considered important safety information and should be collected/reported using the same timeframes and reporting methods as SAEs:

- Exposure to product during pregnancy or lactation
- Lack of effect

Causality Assessment

A causality assessment (attribution) must be performed and recorded for each SAE/non-serious AE in relationship to a Sponsor's product. During studies with direct patient contact (visits), the assessment of causality will be determined by an investigator who is a qualified physician according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product: There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; and the AE is more likely explained by the Sponsor's product than by another cause. In studies without direct patient contact, the assessment of causality would be determined by a notation of attribution in medical records. Causality can be assigned by the investigator or the Sponsor. Examples include a drug-induced rash that an

investigator attributes to a specific product, or a clinical notation that a product was discontinued because it caused insomnia.

Adverse Event Reporting

This is a non-interventional database study. No reporting of individual cases to regulatory agencies is planned. Because there is no access to individual patient/subject charts for this study, no specific attribution of cases is possible. However, if through the conduct of this study, an investigator becomes aware of any Serious Adverse Event (SAE) that is attributed to any investigational or marketed product manufactured by Merck, the INSTITUTION will complete an Adverse Event report form (attachment) in English and submit SAEs within 24 hours and non-serious AEs within 10 calendar days via Fax to Merck Global Safety at PPD (US), or toll-free FAX PPD (ex-US and US availability).

Although NSAEs are not actively solicited in this study, if any attributed NSAEs are reported by the investigator, they must be collected for tabulation in interim and/or final study report and submitted to Global Safety using the method described above.

The end of study report, and any interim analysis, will include aggregate listings of all SAEs and any spontaneously reported NSAEs attributable to etoricoxib and will be provided to regulatory agencies as required. All interim and final study reports will be included in Periodic Safety Update Reports (PSUR's) and/or Development Safety Update Reports (DSUR's) until completion of the study as required.

SAEs and spontaneously reported NSAEs attributable to OTHER investigational or marketed products manufactured by Merck will be collected and reported to regulatory agencies as individual cases as required.

12. Plans for disseminating and communicating study results

The project will be published (i.e. posted at the EU PAS registry per GVP) in a study report encompassing in detail the data sources, data management, analyses and results. The outcomes will also be published in English language peer reviewed journals if possible. The aim is to get publications in a relevant journal focusing on the area of research.

13. References

http://www.medicines.org.uk/emc/medicine/8734#POSOLOGY

http://www.medicines.org.uk/emc/medicine/8734#CONTRAINDICATIONS

www.medstat.dk

http://www.norpd.no/

http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel

http://www.kela.fi/web/en/statistical-database-kelasto

Andersen JS, de Fine Olivarius N, Krasnik A. The Danish national health service register. Scandinavian Journal of Public Health, 2011, 39, 33-37.

Gissler M, Haukka J. Finnish health and social welfare registers in epidemiological research. Norsk Epidemiologi 2004;14:113-120

Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scandinavian Journal of Public Health, 2011, 39, 38-41.

Kimland E, Nydert P, Odlind V, Böttiger V, Lindemalm S. Paediatric drug use with focus on off-label prescriptions at Swedish hospitals – a nationwide study. Acta Pædiatrica, 2012, 101, 772-778

Klaukka T. The Finnish database on drug utilization. Norwegian Journal of Epidemiology, 2001, 11, 19-22.

Roda RP, Bagán JV, Soriano YJ, Romero LG. Use of nonsteroidal anti-inflammatory drugs in dental practice. A review. Medicina Oral Patologia Oral y Cirugia Bucal, 2007, 12, E10-8.

Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving. Scand J Public Health 2011;39:12-16.

Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A non-interventional, population-based register study on the prescription of etoricoxib (Arcoxia®) to dental surgery patients in the Nordic countries

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	7
1.1.2 End of data collection[2]	☒	☐	☐	7
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	7

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6-7, 8-9
2.1.2 The objective(s) of the study?	☒	☐	☐	6-7, 10
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8-9
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	10

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	6, 10
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	10, 11-12
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

The study endpoint is considered to be etoricoxib use

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	11, 12
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	11, 12
4.2.2 Age and sex?	☒	☐	☐	11-12
4.2.3 Country of origin?	☒	☐	☐	11-13
4.2.4 Disease/indication?	☒	☐	☐	11-12
4.2.5 Co-morbidity?	☒	☐	☐	12
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	11

Comments:

Indication is considered to be etoricoxib use Comorbidity is considered to be concomitant medication

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure				

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	11-12
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	16, 17

Comments:

Endpoint is considered to be etoricoxib use

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	11-13
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	11-13
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	11-12
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	12

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	16
10.4 Are stratified analyses included?	☒	☐	☐	16
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	15
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	14-15
11.3 Are methods of quality assurance described?	☒	☐	☐	14-15
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	16-17
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Re. 11.1: It has not be decided how to handle the missing values, but it is stated that the national scientific coordinators should discuss and agree on how to handle missing data

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☐	☒	
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	17
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
12.3 Does the protocol address other limitations?	☒	☐	☐	17

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	14-15

Comments:

Applications for approval of the study will be submitted to The National Data Protection Agencies - Ethical committees should not approve register-based studies in the Nordic countries

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☐	☒	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	20
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	20

Comments:

Name of the main author of the protocol: PPD

Date: 29/6/1

Signature: PPD

Annex 3. Additional information

None