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 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 the duration of use / number of tablets dispensed
Country(-ies) of study	Denmark, Finland, Norway, and Sweden
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Marketing authorisation holder(s)

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

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

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