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Etoricoxib Prescribing Patterns and Adverse Events of Interest during Etoricoxib Treatment in UK Primary Care: an Updated Analysis

PPD

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SUMMARY OF CHANGES TO PROTOCOL

The following changes have been made to the protocol since the last update. Details are found in the relevant sections of the protocol:

- Extended the time period for identification of the first etoricoxib prescription for eligible patients by 18 months to 30 June 2013, to add more patients to the analysis
- Extended the study period (for follow-up of patients) by 18 months to 30 June 2014, to add more follow-up time to the analysis
- Updated drug code lists based on updates to British National Formulary

Comparison of some results from this analysis to the previous analysis should be done cautiously, because changes in GP practice patterns and changes in the characteristics of the patient population prescribed NSAIDs and COX-2 inhibitors over time makes comparisons of these results to those of the prior analyses difficult. In addition, changes to the drug code lists may result in changes in the results that are a function of coding changes rather than changes in prescribing patterns.

1.0 BACKGROUND

The selective COX-2 inhibitors ('coxibs') were developed to minimize the gastrointestinal (GI) toxicity associated with traditional non-selective NSAIDs [Langman et al., 2000; Lazzaroni & Bianchi Porro, 2004]. A recent study of the CPRD showed that the selective COX-2 inhibitors celecoxib and rofecoxib were preferentially prescribed (i.e. "channeled") to patients with a previous history of upper GI symptoms compared to traditional non-selective NSAIDs (MacDonald et al., 2003) in accordance with the prescribing guidance issued by the National Institute for Clinical Excellence (NICE, 2001). Etoricoxib is a selective COX-2 inhibitor that was approved in the UK in April 2002 for the treatment of osteoarthritis, rheumatoid arthritis, and acute gouty arthritis. Following the voluntary worldwide withdrawal of rofecoxib on 30 September 2004 and the publicity regarding an increased risk of thrombotic cardiovascular events among patients randomized to celecoxib versus placebo in the US National Cancer Institute (NCI) Adenoma Prevention with Celecoxib (APC) trial on 17 December 2004, the Chairman of the Committee on the Safety of Medicines (CSM) and the Medicines and Health Care Products Regulatory Agency (MHRA) issued a joint letter on 21 December 2004 with the following advice to UK prescribers (CSM, 2004):

- Patients treated with any COX-2 inhibitor who have established ischemic heart disease or cerebrovascular disease should be switched to alternative (non-COX-2 selective) treatments as soon as is convenient.

- For all patients, alternative treatments should be considered in light of an individual assessment of risks and benefits of COX-2 inhibitors, in particular cardiovascular, gastrointestinal and other risk factors.

- Prescribers are reminded that for all NSAIDs (including COX-2 inhibitors), the lowest effective dose should be used, for the shortest duration necessary.

On 17 February 2005, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) issued an Urgent Safety Restriction on the use of COX-2 selective inhibitors that included additional prescribing advice (CSM, 2005a; EMEA, 2005a):

- The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.

- As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

- New contraindications for all selective COX-2 inhibitors in patients with established ischemic heart disease or cerebrovascular disease

- The existing contraindication for severe heart failure is now extended to include moderate heart failure (NYHA classes II-IV, moderate/severe heart failure)

- A contraindication specifically for etoricoxib for patients whose blood pressure has not been adequately controlled.

- The Urgent Safety Restriction included additional Special Warnings and Precautions concerning increased risk of gastrointestinal adverse effects, thrombotic events, as well as advice that patients with significant risk factors for cardiovascular events should only be treated after careful consideration, and that careful monitoring of blood pressure is advised for patients taking etoricoxib, and that alternative treatment should be considered if blood pressure increases significantly.

- An additional drug interaction description about the potential for NSAIDs to reduce the antihypertensive effect of antihypertensive drugs was also incorporated into the product circular at this time.

The CHMP review of COX-2 selective inhibitors safety concluded in June 2005 with recommended additional revisions to product labeling that were published on the EMEA internet web site. The CHMP recommended maintenance of the Marketing Authorizations for the selective COX-2 inhibitors (including etoricoxib) for the

indications stated in their respective product circulars. The European Commission adopted the CHMP's conclusions and proposed revised labeling for selective COX-2 inhibitors in November 2005.

When prescribed in accordance with the aforementioned contraindications and precautions, the CHMP concluded that the balance of benefits and risks remains positive for the coxibs when used in their target populations (EMEA, 2005b; 2005c).

In 2007 and 2008, in the context of the evaluation of the application for extension of the indication for ARCOXIA use to include Ankylosing Spondylitis (AS), concerns were raised over the cardiovascular safety of etoricoxib-containing medicines when used to treat AS at a dose of 90 mg once a day. These concerns also extended to the treatment of rheumatoid arthritis (RA) which is used at the same dose. In June of 2008, upon finalizing a review of the benefits and risks of etoricoxib-containing medicines, the CHMP / EMEA concluded that these medicines can be used to treat RA and AS. During the review, the CHMP concluded that the benefits of etoricoxib-containing medicines outweigh their risks for the treatment of RA and AS when used at a dose of 90 mg once a day and therefore recommended that the extension of indication for ARCOXIA to include AS be granted and that the indication in RA could be maintained. However, the Committee recommended updating the existing contraindication in patients with hypertension that is not adequately controlled to state that patients whose blood pressure is persistently above 140/90 mmHg and has not been adequately controlled should not take the medicine. In addition, the CHMP concluded that warnings should be added to the product information for etoricoxib-containing medicines, stating that high blood pressure should be controlled before treatment is begun and should be monitored for two weeks after the start of treatment and regularly thereafter. Finally, the Committee recommended that doctors should prescribe etoricoxib-containing medicines according to the updated product information. Doctors and patients are advised to monitor closely any signs or symptoms of cardiovascular side effects.

This study was originally conducted as a post-licensure commitment to the EMEA to

- Describe the characteristics of new and continuing users of etoricoxib in the UK who were prescribed this drug before and after the first EMEA guidance was issued on 17 February 2005.

- Describe the extent of repeat prescribing for etoricoxib before and after 17 February 2005.

The current protocol is an update to the previous version to include additional patients and follow-up time by extending the time period for identification of the first etoricoxib prescription for eligible patients one year, and extending the study period one year to 31 December 2012. In the current protocol, drug code lists are also updated from the original protocol.

2.0 PURPOSE

The characteristics of new users of etoricoxib at the date of each patient's first GP-issued etoricoxib prescription will be described in two sub-cohorts of the study population defined by the calendar period of the first etoricoxib prescription:

- 1 April 2002 to 17 February 2005
- 18 February 2005 to 30 June 2013

The characteristics of continuing users of etoricoxib at the date of their first repeat etoricoxib prescription issued after 17 February 2005 also will be described. A continuing etoricoxib user will be defined as patient who was issued one or more etoricoxib prescriptions on or before 17 February 2005 and at least one etoricoxib prescription after this date.

3.0 SPECIFIC OBJECTIVES

The specific objectives of this descriptive study are to describe:

a. The characteristics of new users of etoricoxib before and after 17 February 2005 among patient subgroups defined by age group, sex, starting dose and inferred indication.

b. The characteristics of continuing users of etoricoxib at the date of their first repeat etoricoxib prescription issued after 17 February 2005 among patient subgroups defined by age group, sex, dose, and inferred indication.

c. The distribution of etoricoxib repeat prescribing over a 1-year period from patients' first GP-issued etoricoxib prescription among subgroups of new users before and after 17 February 2005 defined by age group, sex, starting dose and inferred indication.

d. The distribution of the total duration of etoricoxib repeat prescribing from the date of each patient's first prescription to the date of his/her last prescription recorded in the CPRD at the date of query execution among subgroups of new users before and after 17 February 2005 stratified by age group, sex, starting dose and inferred indication.

e. The absolute incidence rate of GI, edema, acute renal impairment/failure, hypertension, heart failure and vascular AEs of interest and sudden / unexplained death during periods of assumed etoricoxib treatment among subgroups of new users before and after 17 February 2005 defined by age group, sex, starting dose and inferred indication.

f. The proportion of patients whose GP had either increased or decreased the daily dose of etoricoxib relative to the starting dose within the first year after patients' first GP-issued etoricoxib prescription among subgroups of new users before and after 17 February 2005 defined by age group, sex, starting dose and inferred indication.

4.0 STUDY POPULATION

The study population will include all patients in the MHRA's Full Feature CPRD (FF-CPRD) who have at least one electronic outpatient prescription record for etoricoxib issued during the period (1 April 2002 to 30 June 2013) at the date of query execution against the FF-CPRD data warehouse.

Patients prescribed etoricoxib during the study period will be excluded from the analysis of patient characteristics for any of the following administrative reasons:

i. Patient was not registered with a CPRD-contributing practice that had continuously collected data deemed to be 'up-to-standard' for research purposes from 1 April 2002 through to 30 June 2014.

ii. Patient was never registered as a permanent patient of a GP in the practice.

iii. Patient's registration details were not acceptable (i.e., incomplete data on patient's sex, birth year or registration date, or logically implausible dates of death or transferral out of the practice relative to the patients' registration date).

iv. Patient had not been registered with a GP for at least 365-days before the date of his/her first etoricoxib prescription recorded in the CPRD.

5.0 STUDY DESIGN

The characteristics of new users of etoricoxib at the date of each patient's first GP-issued etoricoxib prescription will be described in two sub-cohorts of the study population defined by the calendar period of the first etoricoxib prescription:

- 1 April 2002 to 17 February 2005
- 18 February 2005 to 30 June 2013

The characteristics of continuing users of etoricoxib at the date of their first repeat etoricoxib prescription issued after 17 February 2005 also will be described. Etoricoxib repeat prescribing within a 1-year period from each patient's first etoricoxib prescription will be described among patients who began therapy before and after 17 February 2005 using a historical cohort study design. A standard 1-year follow-up period will be used to

descriptively compare repeat prescribing patterns across the two groups in order to avoid bias introduced by different lengths of follow-up.

The duration of etoricoxib repeat prescribing in each of the two groups at the date of query execution on the FF-CPRD data warehouse also will be described using a historical cohort study design.

Analyses of AEs of interest during assumed treatment with etoricoxib will be conducted using a historical cohort study design in which etoricoxib exposure status is allowed to vary over the course of follow-up in accordance with the dates of etoricoxib prescriptions in each patient's chronological CPRD record. The treatment emergent AE's would be the subset of events that occurred while patients were assumed to be "current users" of etoricoxib during the course of follow-up. Patients who have a prior medical history of an AE of interest code in their CPRD electronic medical record before the date of their first etoricoxib prescription will be identified. For each type of AE, analyses will be done separately in patients with and without a prior medical history of that event. Follow-up will end on the earliest of the occurrence of the specific AE, death, transfer of the patient to another practice, or the end of the study period (30 June 2014). It should be noted that given the design of this study, interpretation of the results of such analyses in patients with a prior history of a given type of event is very difficult.

6.0 SELECTION OF CONTROLS

Not applicable

7.0 CLINICAL OUTCOMES OF INTEREST

Newly incident GI, edema, acute renal impairment/failure, hypertension, heart failure, vascular AEs of interest, sudden / unexplained death, and new prescriptions for GI and CV medications during periods of etoricoxib treatment will be defined by Read and BNF codes recorded in patients' electronic medical records, as follows:

- Gastrointestinal Ulcer, Perforation and Bleeding (Appendix 5)
- Gastroprotective medication (BNF chapters 1.3.1 H2-receptor antagonists; 1.3.4 prostaglandin analogues; 1.3.5 proton pump inhibitors; 1.3.6 other ulcer-healing drugs).
- Edema (Appendix 7)
- Acute renal impairment / failure (Appendix 26)
- Heart failure / left ventricular dysfunction (Appendix 8)

- Acute thromboembolic cardiovascular events
    - Acute myocardial infarction (Appendix 9)
    - Unstable angina pectoris (Appendix 10)

A fatal acute thromboembolic cardiovascular event will be defined operationally by the instance of a CHD code recorded on or after the date of a death code in the patient's electronic medical record.

- Acute hemorrhagic / thromboembolic cerebrovascular events
    - Cerebral infarction (Appendix 12)
    - Cerebrovascular accident not otherwise specified (Appendix 13)
    - Intracerebral hemorrhage / subdural bleed (Appendix 14)
    - Transient ischemic attack (Appendix 15).

A fatal cerebrovascular event will be defined operationally by the instance of a cerebrovascular code recorded on or after the date of a death code in the patient's electronic medical record.

- Deep venous thrombosis (Appendix 22)
- Pulmonary embolism (Appendix 23)

A fatal pulmonary embolism will be defined operationally by the instance of a pulmonary embolism code recorded on or after the date of a death code in the patient's electronic medical record.

- Arterial embolism / thrombosis (Appendix 16)
- Sudden or unexplained death (Appendix 21)
- Cardiovascular medication (BNF chapters: 2.1.1 cardiac glycosides; 2.2 diuretics; 2.4 beta-blockers; 2.5.5.1 ace inhibitors; 2.5.5.2 angiotensin-II receptor antagonists; 2.6.1 nitrates; 2.6.2 calcium-channel blockers; 2.8.2 oral anticoagulants; 2.9 oral antiplatelet drugs; 2.12.1 anion-exchange resins; 2.12.2 ezetimibe; 2.12.3 fibrates; 2.12.4 statins; 2.12.5 nicotinic acid).
- Hypertension diagnosis (Appendix 18)

- Hypertensive diagnosis + hypertension medication (the combination of a code that qualifies as a hypertension diagnosis in Appendix 18, and a prescription within 90 days of the diagnosis date for antihypertensive medication: including diuretic [BNF chapter 2.2], beta-blocker [BNF chapter 2.4], angiotensin-converting enzyme (ACE) inhibitor; BNF chapter 2.5.5.1], angiotensin-II receptor antagonist [BNF chapter 2.5.5.2], or calcium-channel blocker [BNF chapter 2.6.2]). N.B. It has been shown that to identify patients with hypertension in a claims database a selection rule using both a diagnosis and prescription claim has greater sensitivity and specificity than a rule using a diagnosis claim only. (Bullano 2006).

- Blood pressure measurement – the recording of a blood pressure measurement in the patient record

We do not plan to request hospital discharge summaries to validate the diagnostic criteria and date of first onset for these target AE's.

8.0 NON-CLINICAL OUTCOMES OF INTEREST

The non-clinical outcome of interest will be GP prescribing patterns for the following licensed product forms of etoricoxib listed in the British National Formulary (BNF) as of the end of the study period:

- 30-mg and 60-mg tablets (28-tablet pack) – licensed dose for osteoarthritis

- 90-mg tablets (28-tablet pack) – licensed dose for rheumatoid arthritis

- 90-mg tables (90-mg tablets (28-tablet pack) – licensed dose for ankylosing spondylitis

- 120-mg tablets (7-tablet or 28-tablet pack) – licensed dose for acute gout

Etoricoxib repeat prescribing will be measured by the total number of days of intended etoricoxib treatment prescribed over a 365-day follow-up period beginning on the date the index etoricoxib prescription (first-ever prescription or first prescription issued after 17 February 2005). The number of days of intended etoricoxib therapy prescribed during this 365-day follow-up period will be estimated from the quantity of packs prescribed, the number of tablets supplied in each pack, and the dosing instructions recorded with each prescription translated into an average daily dose using an algorithm developed by the CPRD Division of the MHRA (Shah & Martinez, 2003). The World Health Organization defined daily dose (DDD) of one tablet per day for etoricoxib will be assumed when the daily dose cannot be deduced from the dosing instructions entered with a prescription (e.g., PRN use such as 'take 1-2 daily when required'), or when the dosing instructions have been deleted (anonymized) by CPRD Division to protect patient privacy. A sensitivity analysis will be conducted to evaluate the impact of this assumption in

determining the distribution of etoricoxib treatment days prescribed over a 1-year period. If the number of treatment days included with the last etoricoxib prescription exceeds the 365th day of follow-up, then the duration of the last prescription will be truncated at the quantity of tablets that the patient should have used by the 365th day of follow-up.

The total duration of etoricoxib repeat prescribing will be estimated as the difference in days between the date of the first and last etoricoxib prescription recorded in the CPRD for each patient as of the date of query execution against the FF-CPRD data warehouse. The medication possession ratio (MPR) will be estimated as the ratio of the number of days of etoricoxib repeat prescribing as defined above.

In view that this proposed study will measure GP prescribing and not actual drug use by patients, any inferences about drug utilization by patients will require that the following set of assumptions all hold true: 1) all prescriptions were dispensed to patients on the same day that they were issued by each practice's computer system; 2) patients consumed etoricoxib as directed on consecutive days after the date that each prescription was issued; and 3) patients consumed the entire quantity of drug supplied in each prescription. The CPRD does not capture prescriptions issued by hospital-based specialists (e.g., consultant rheumatologists). Hence, this study only will measure the quantity of etoricoxib prescribed by GP's, and not all health care providers in the UK National Health Service (NHS). The limitations of inferring actual NSAID use from GP prescribing data recorded in electronic databases has been reviewed elsewhere (Ilkhanoff et al., 2005)

9.0 BASELINE CHARACTERISTICS OF INTEREST

Demographic Variables

- Gender – categorical [men, women] – *stratification variable*
- Age – continuous [years]

  – categorical [<65 years, ≥65 years] – *stratification variable*

In 2014, all of the drug code lists were updated based on changes to the BNF. Efforts were made to stay as consistent as possible with the intent of the original drug code lists. In general, drug codes included in previous years were included even if they had been moved to another chapter, and new drugs in a chapter were added if they fit the category.

Medications for musculoskeletal and joint diseases

(Prescriptions issued 1-365 days before the date of the index etoricoxib prescription):

- Other coxibs (celecoxib, rofecoxib, parecoxib, valdecoxib, and lumiracoxib).

- Other NSAIDs regarded as COX-2 selective by NICE (etodolac and meloxicam) (NICE 2001)

- Non-selective NSAIDs defined as any of the following non-aspirin / non-salicylate drugs listed in BNF chapter 10.1.1 (aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, diclofenac, diflunisal, fenbufen, fenoprofen, feprazone, flurbiprofen, ibuprofen, indomethacin, ketoprofen, lornoxicam mefenamic acid, nabumetone, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, and tiaprofenic acid, tolfenamic acid, and tolmetin)

- Aspirin (≥300-mg/tablet formulations of aspirin, benorilate, and co-codaprin) listed in BNF chapters 4.7.1.

- Paracetamol (acetaminophen, including combination products) listed in BNF chapter 4.7.1

- Narcotic analgesics defined as any drug listed in BNF chapter 4.7.2.

- Disease-modifying anti-rheumatic drugs (DMARDs) defined as any drug listed in BNF chapter 10.1.3. This category includes the following drugs: auranofin, azathioprine, chloroquine, ciclosporin, hydroxychloroquine, leflunomide, methotrexate, penicillamine, sodium aurothiomalate, sulfasalazine.

- TNF inhibitors defined as any drug listed in BNF chapters 10.1.3 and 13.5.3 (drugs that suppress the rheumatic disease process; cytokine modulators in rheumatic disease; drugs affecting the immune response). The code list has included other biologics for the treatment of rheumatic diseases since the inception of the study. It has been updated in 2014 and now includes the following: adalimumab, anakinra, certolizumab, etanercept, golimumab, inflicimab, rituximab, tocilizumab, ustekinumab.

- Drugs used in long-term control of gout defined as any drug listed in BNF chapter 10.1.4 which is specifically i which is specifically indicated for long-term control, plus colchicine which was previously included, but no long is identified as being for long-term control.

- Oral corticosteroids defined as any oral formulation of a drug listed in BNF chapter 6.3.2.

- Immune suppressants in chapter BNF 8.2.2. This only includes ciclosporin, sirolimus, and tacrolimus.

- Local and parenteral corticosteroid injections defined as any formulation for injection of a drug listed in BNF chapter 10.1.2.2.

Gastrointestinal medications

(Prescriptions issued 1-365 days before the date of the index etoricoxib prescription):

- Antacids defined as any preparation listed in BNF chapter 1.1.1. This excludes 1.1.1.4 (simeticone alone) and 1.1.1.05 (sodium citrate).

- H2-receptor antagonists defined as any drug listed in BNF chapter 1.3.1.

- Prostaglandin analogues defined as any drug listed in BNF chapter 1.3.4 and any product that combined misoprostol with an NSAID. Manual search was included to insure that all NSAID / misoprostol combinations were included.

- Proton pump inhibitors defined as any drug listed in BNF chapter 1.3.5.

- Other ulcer-healing drugs defined as any drug listed in BNF chapter 1.3.6. Manual search was employed to include products with carbenoxolone and pyrogastrone which were previously included.

Patients will be classified as having a coded medical history of the following conditions as of the date of the index etoricoxib prescription if the date of the coded entry in their respective electronic medical records precedes or coincides with the date of their index etoricoxib prescription. Historical entries that have a missing date value will be assumed to have been diagnosed at the date of the index etoricoxib prescription.

Musculoskeletal Disease (inferred indications for etoricoxib use)

(A coded entry recorded at any time in a patient's electronic medical history – see Data Analysis)

- Osteoarthritis (Appendix 1)

- Rheumatoid arthritis (Appendix 2)

- Gouty arthritis (Appendix 3)

- More than one specific type of arthritis defined above

- Arthritis not otherwise specified as OA, RA or Gout (Appendix 4)

- Ankylosing Spondylitis (Appendix 24)

- None of the above indications

Gastrointestinal Ulcer, Perforation and Bleeding (Appendix 5)

Kidney disease (Appendix 6)

Acute Renal Failure / impairment (Appendix 26)

Edema (Appendix 7)

Heart failure or Left ventricular dysfunction (Appendix 8)

Coronary Heart Disease

- Myocardial infarction (Appendix 9)
- Unstable angina pectoris (Appendix 10)
- Subacute coronary heart disease (other than MI or unstable angina pectoris) (Appendix 11)

Cerebrovascular Disease

- Cerebral infarction (Appendix 12)
- Cerebrovascular accident not otherwise specified (Appendix 13)
- Intracerebral hemorrhage / subdural bleed (Appendix 14)
- Transient ischemic attack (Appendix 15)

Peripheral Arterial Disease

- Arterial embolism / thrombosis (Appendix 16)
- Intermittent claudication (Appendix 25)
- Peripheral vascular disease not otherwise specified (Appendix 17)

Deep venous thrombosis (Appendix 22)

Pulmonary embolism (Appendix 23)

Atherosclerotic cardiovascular disease (Appendix 27)

Hypertension diagnosis (Appendix 18)

Dyslipidemia (Appendix 19)

Diabetes mellitus (defined by any of the following criteria):

- Diabetes diagnostic code (Appendix 20)
- Insulin prescribed prior to index date (any insulin preparation listed in BNF chapter 6.1.1). The code list was corrected in 2014 to exclude items in the BNF chapter that were strictly devices (empty syringes, test strips)
- Oral antidiabetic agent prescribed prior to index date (any product listed in BNF chapter 6.1.2)

Cardiovascular Risk Factors

The last recorded observation of smoking status and body mass index will be carried forward to the date of the index etoricoxib prescription:

Smoking status

– categorical [non-smoker, current smoker, ex-smoker, missing; the number and percent of patients with data missing will be enumerated]

Body mass index (BMI)

– continuous [kg/m2]

– categorical [<20, 20-24, 25-29, ≥30 kg/m2, missing; the number and percent of patients with data missing will be enumerated]]

Systolic blood pressure (SBP); the number of blood pressure measurements taken in the 6 months prior to the index prescription and the specific details of the last measurement prior to the index prescription will be described.

– continuous [mm Hg]

– categorical [<140, 140-149, 150-159, ≥160 mm Hg, missing; the number and percent of patients with data missing will be enumerated]]

Diastolic blood pressure (DBP)

– continuous [mm Hg]

– categorical [<90, ≥90 mm Hg, missing; the number and percent of patients with data missing will be enumerated]]

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Cardiovascular medications (categorized by BNF chapter)

(Any prescription issued 1-365 days before the date of the index etoricoxib prescription):

2.1.1 Cardiac glycosides

2.2 Diuretics

2.4 Beta-blockers

2.5.5.1 Angiotensin-converting enzyme (ACE) inhibitors 2.5.5.2 Angiotensin-II receptor antagonists

2.6.1 Nitrates 2.6.2 Calcium-channel blockers

2.9 Oral antiplatelet drugs (including low-dosage (<300 mg) forms of aspirin). In 2014, this list was updated to include the more recently approved anti-platelets (e.g., dabigatran, rivoroxaban, apixaban)

2.12.1 Anion-exchange resins

2.12.2 Ezetimibe

2.12.3 Fibrates

2.12.4 Statins

2.12.5 Nicotinic acid

10.0 DATA ANALYSIS

All data analyses will be purely descriptive and no statistical hypothesis testing will be conducted in this observational study.

Patient Characteristics

The characteristics of new users of etoricoxib will be measured at the date of each patient's first GP-issued etoricoxib prescription in sub-cohorts of the study population defined by calendar period of the first etoricoxib prescription:

- 1 April 2002 to 17 February 2005
- 18 February 2005 to 30 June 2013.

The characteristics of new users of etoricoxib will be described among different patient subgroups within each calendar period categorized by age group, sex, starting dose, and inferred indication.

The characteristics of continuing users of etoricoxib will be described at the date of their first etoricoxib prescription issued after 17 February 2005. The characteristics of continuing users also will be described among different patient subgroups defined by age group, sex, starting dose, and inferred indication.

The proportion of patients in each nominal level will be determined for all categorical variables. Means, standard deviations, medians, inter-quartile ranges, minimum and maximum values will be calculated to describe the distribution of each continuous variables among the subset of patients who have non-missing data for that variable. Select continuous variables (age, calendar time, BMI, and blood pressure) also will be analyzed as categorical variables using the cut-points defined above.

The proportion of patients who have a coded medical history of a specific medical condition (e.g., myocardial infarction) at the date of the index etoricoxib prescription will be determined by enumerating the number of patients with an entry in their electronic medical records with any code listed in the Appendix for that specific medical condition (see above) with a date-stamp that precedes or coincides with the date of the index etoricoxib prescription. Entries in patients' computerized medical records that contain an OXMIS/READ code for a target medical condition, but that have a missing date value, will be assumed to have been diagnosed at the date of the index etoricoxib prescription.

The proportion of patients prescribed a drug listed in a specific class of medications within the past year will be determined by calculating the number of patients in the sample with one or more computerized outpatient prescription records for a drug in that specific medication class issued 1-365 days before the date of the index etoricoxib prescription. The distribution of the number of different NSAIDs prescribed in the 1-year period preceding the date of the first etoricoxib prescription also will be described for each new user cohort.

Measurements of lifestyle factors (current smoking status, BMI) will be determined from the last observation of these variables recorded on or before the date of each patient's index etoricoxib prescription. The number of blood pressure measurements taken in the 6 months prior to the index prescription and the specific details of the last measurement prior to the index prescription will be described. Patients who do not have at least one valid blood pressure measurement recorded during this 6-month time window will be categorized as having 'missing data' in the analysis.

The number of blood pressure recordings during intended etoricoxib treatment will also be enumerated. These will consist of measurements on dates during intended etoricoxib treatment. Analyses of BP measures during intended etoricoxib treatment in each sub-

cohort defined by calendar time will be done using both the 1-year follow-up (1 year following the date of the index etoricoxib prescription) and the entire available follow-up data. However, descriptive comparisons of BP measures during intended etoricoxib treatment among the samples will be made using the 1-year follow-up data in order to avoid bias introduced by differences in follow-up time in the samples.

Incidence of Clinical Outcomes

New cases of GI events, edema, acute renal impairment/failure, and cardiovascular events of interest while patients were assumed to be on etoricoxib treatment will be identified. Follow-up will end on the earliest of the occurrence of the specific event, death, transfer of the patient to another practice, or the end of the study period (30 June 2014). The occurrence of an event will censor the patient from further analysis of that event. For each type of AE, analyses will be done separately in patients with and without a prior medical history of that event. Analyses will also be conducted with coronary heart disease or sudden / unexplained death, and cerebrovascular disease outcomes combined. These analyses will be also done separately in patients with and without a prior medical history of any of the included types of events.

Analyses of events during intended etoricoxib treatment in each sub-cohort will be done using both the 1-year follow-up (1 year following the date of the index etoricoxib prescription) and the entire available follow-up data. However, descriptive comparisons of events during intended etoricoxib treatment among the samples will be made using the 1-year follow-up data in order to avoid potential bias introduced by different lengths of follow-up time between the two historical cohorts if the hazard function for a specific event is not constant over time. It should be noted that given the design of this study, interpretation of the results of such analyses in patients with a prior history of a given type of event is very difficult. However, the results will inform the feasibility of comparative study designs.

For the 1-year follow-up data, two approaches to the analyses of incidence rates of the above outcomes will be performed. One applies to the first course of new etoricoxib treatment only and the other applies to all courses of etoricoxib treatment during the follow-up. For the entire available follow-up data, incidence rates for all courses of etoricoxib treatment will be calculated, and if it is found that a significant number of patients' first course of etoricoxib treatment lasts longer than one year, incidence rate for the first course will also be calculated.

The number of patients whose GP had initiated GI and cardiovascular medications during periods of assumed etoricoxib use also will be determined. Follow-up will end on the earliest of the occurrence of the specific prescription, death, transfer of the patient to another practice, or the end of the study period (30 June 2014). The occurrence of a prescription will censor the patient from further analysis of that event. Analyses of prescriptions during intended etoricoxib treatment will be done using both the 1-year

follow-up (1 year following the date of the index etoricoxib prescription) and the entire available follow-up data. However, descriptive comparisons of newly initiated therapy during intended etoricoxib treatment among the samples will be made using the 1-year follow-up data in order to avoid potential bias introduced by different lengths of follow-up time between the two historical cohorts if the hazard function for a specific event is not constant over time.

For all above analyses, etoricoxib use will be considered current if a patient was in a course of etoricoxib treatment. A course of treatment starts from the date of prescription and ends at prescription duration plus 14 days. Patients with missing data on duration of a prescription will be assigned the median value for this parameter for their specific indication. If another prescription of etoricoxib is recorded while the previous prescription is still current, the course of treatment will be considered as continuing, and so on until the supply end date for the last prescription in the course of therapy or the end of follow-up. If a prescription for a COX-2 inhibitor other than etoricoxib or a prescription for another NSAID occurs before the end of a course of etoricoxib treatment, we will assume the patient stopped using etoricoxib on the day of new prescription of the other COX-2 inhibitor/NSAID. To examine the validity of this assumption, we will do a sensitivity analysis without this assumption.

For the 2015 report, MHRA asked the MAH to conduct some additional analyses to 1) describe characteristics and health outcomes of interest in OA and RA patients taking standard doses and those taking higher than labelled doses, and 2) describe characteristics and health outcomes over time in Sub-cohort 2.

Algorithm for Inferring Indication

The Vision software that underlies electronic data collection system for the CPRD does not use a problem-oriented medical record (POMR) to link specific diagnoses with specific prescriptions (Carey et al., 2003). Instead, the indications for specific prescriptions must be inferred from the READ codes that GP's enter during the same consultation as a prescription (i.e., on the same calendar date). The CPRD Recording Guidelines ask GP's to record the indication for every acute prescription issued during a consultation. The indication for repeat prescriptions only needs to be recorded on the date of creating a repeat master file for a drug.

The codes typically recorded during GP consultations usually correspond to patient complaints (e.g., joint pain), and hence, these codes may not be informative in regards to the actual medical diagnosis (e.g., osteoarthritis). We will produce a frequency table of all READ codes entered on the same date as each patient's first GP-issued etoricoxib prescription to rank the most frequent medical codes associated with patients' first prescription for etoricoxib similar to other NSAID utilization reviews (Oregon State University, 2001).

In view of the anticipated incompleteness of medical diagnosis coding versus symptom coding in the CPRD, a hierarchical strategy will be implemented to infer the actual medical diagnosis for prescribing etoricoxib to each patient. First, all patients who have a coded entry for osteoarthritis (OA), rheumatoid arthritis (RA), gout, or ankylosing spondylitis (see Appendices 2, 3, 4, and 24 respectively) recorded on the same date as their first GP-issued etoricoxib prescription will be identified and classified accordingly (Level 1 inference). For the remaining patients, we will identify patients who had a coded entry for OA, RA gout, or ankylosing spondylitis recorded on the same day as a subsequent repeat etoricoxib prescription (Level 2 inference). If no READ code for OA, RA, gout, or ankylosing spondylitis was ever entered on the same day as an etoricoxib prescription, then the intended indication will be inferred from entries of OA, RA, gout or ankylosing spondylitis codes recorded at any time in patients' computerized medical records (Level 3 inference). Patients will be classified as having 'more than one specific type of arthritis' whenever codes from two or more code lists for OA, RA or gout are found at the same inference level.

The electronic medical records of patients who still remain unclassified with respect to a coded indication of OA, RA, gout, or ankylosing spondylitis will be searched for OXMIS/READ codes corresponding to 'non-specific arthritis' terms (see Appendix 4). The hierarchical strategy for classifying patients with respect to a diagnosis of 'non-specific arthritis' in association with an etoricoxib prescription will proceed as stated above for the three target indications of OA, RA and gout.

Patients who do not have a coded entry corresponding to any arthritis-related term at any time in their electronic medical records will be classified as 'unknown' with respect to the indication for prescribing etoricoxib.

Repeat Etoricoxib Prescribing

Patients who have less than 365-days of follow-up after the date of their index etoricoxib prescription (first-ever prescription or first prescription issued after 17 February 2005) will be excluded from the analysis of repeat prescribing over a subsequent 1-year period of observation. Repeat etoricoxib prescribing over a 1-year period of follow-up from the date of the index etoricoxib prescription (first-ever prescription or first prescription issued after 17 February 2005) will be described by calculating the median, inter-quartile range, minimum and maximum values of the estimated number of days of etoricoxib therapy prescribed by GP's over this 1-year observation period similar to other NSAID utilization studies published in the literature (Cox et al., 2003; Moore et al., 2004). The distribution of the number of days of etoricoxib therapy prescribed by GP's during this 1-year follow-up period will be described for the entire study population and for patient subgroups stratified by new versus continuing use, age group, sex, dose and inferred indication. This analysis will be done using all patients in the cohorts as well as restricted to patients who didn't switch to other COX-2 inhibitor or other NSAIDs. When doing this analysis stratified by dose, patients will be excluded if they switched from one dose

to another. For the users who switched doses of etoricoxib, patients' characteristics as well as switching pattern will be described. A sensitivity analysis will recalculate the distribution of etoricoxib treatment days prescribed over a 1-year period using only patients who have interpretable dosing instructions recorded with all of their etoricoxib prescriptions issued during the 1-year follow-up period. Other analytic techniques may also be used to examine the data depending upon the results.

The distribution of the duration of etoricoxib use will be described by calculating the median, inter-quartile range, minimum and maximum values of the difference in days between the dates of each patient's first and last etoricoxib prescription recorded in the CPRD at the date of query execution against the FF-CPRD data warehouse. The medication possession ratio (MPR) will be calculated as the ratio of the number of days of etoricoxib treatment prescribed over the duration of etoricoxib use. The numbers and percentages of patients using etoricoxib continuously for various time intervals (e.g., 6, 12, 18, and 24 or more months) will be calculated. Other analytic techniques may also be used to examine the data depending upon the results.

Changes in dose over time will be described, by patient and indication, in each sub-cohort using both the 1-year follow-up (1 year following the date of the index etoricoxib prescription) and the entire available follow-up data. If the data indicate that there are substantial numbers of patients with increases in dose, further analyses may be undertaken to understand the effects of duration of therapy and other factors to the changes in dose.

11.0 STUDY PERIOD

The study period for the analysis will commence on 1 April 2001 and will end on30 June 2014.

12.0 OBSERVATIONAL PERIOD

The date of the first GP-issued etoricoxib prescription will define each patient's start date of follow-up for evaluating repeat etoricoxib prescribing over a subsequent 1-year period of observation in the analysis of new users. The date of the first etoricoxib prescription issued after 17 February 2005 will define each patient's start date of follow-up for evaluating repeat etoricoxib prescribing over a subsequent 1-year observation period for continuing users. Patients who do not have 365-days of subsequent follow-up will be excluded from the analysis of repeat prescribing over the first year of therapy. A patient's last day of follow-up will be defined as the *earliest* of the following dates:

- Date of death.
- Date of transfer out of the practice

- Date of the last data collection from the practice
- Last day of the study period (30 June 2014)

13.0 REPORTING OF SERIOUS ADVERSE EVENTS

No reporting to regulatory agencies of individual Serious Adverse Events (SAE) is planned as part of this retrospective observational database study. This is consistent with Council for International Organizations of Medical Sciences (CIOMS) V, which states that for epidemiological studies, individual case reporting is generally not appropriate unless there is specific attribution of an individual case (i.e., within the medical record). The study results will be included in a report at the end of study. Interim reports may be provided on an annual basis to the regulatory agencies until completion of the study. Aggregate reports may be provided to regulatory agencies in the Periodic Safety Update Reports (PSUR) as soon as available.

Evaluation of individual cases is not a planned component of this retrospective observational database study. In the event an evaluation is required for a specific health outcome of interest, the protocol would be amended or the evaluation would be conducted under a separate protocol and the results would be summarized in a report aggregating the data.

14.0 POTENTIAL LIMITATIONS

Our drug exposure ascertainment method based on GP prescribing data (rather than on pharmacy dispensing data or on actual patient observation) will be expected to over-estimate actual use of etoricoxib in the study population because a significant proportion of patients are known to never fill their prescriptions (de Vries et al., 2000). Furthermore, among patients who do fill their prescriptions, many do not consume the entire quantity of tablets dispensed to them, which also will contribute to an over-estimation of actual etoricoxib use in our study population (Girvin & McGavock, 2000; Hughes et al., 2001). Due to privacy concerns, it is not possible to link electronic prescribing data in the CPRD with prescribing analysis and cost (PACT) dispensing data from the Prescription Pricing Authority at the practice level to assess the extent of primary non-adherence in our study population (Ferguson, 2000). Prescriptions issued outside of a patient's primary care practice by hospital-based specialists also are not captured in the CPRD.

Sample selection bias is possible to the extent that the prescribing behavior of the GP's in our study sample is not representative of the prescribing behavior of all GP's in the UK.

The indication for prescribing etoricoxib may be subject to considerable measurement error due to variation in the specificity and completeness of GP coding of musculoskeletal diseases in UK primary care (Connolly and McGavock, 2000).

Furthermore, the changes in electronic data recording in UK primary care that have taken place in response to the new GMS contract may also affect prevalence estimates of specific diagnoses over time.

The CPRD does not capture data on the reason why a GP decides to switch a patient from one NSAID to another in a systematic manner. Therefore, it is not possible to determine the proportion of patients prescribed etoricoxib who were deemed to be intolerant to non-selective NSAIDs in our study population.

The code-based operational definitions for the AE's of interest may overestimate the true occurrence of newly incident AE's due to the fact that some codes are entered as provisional diagnoses for hospital referrals which are later refuted by further diagnostic testing performed at the hospital.

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17.0 LIST OF APPENDICES

The following appendices containing diagnosis codes used in this protocol are found under separate cover:

Appendix Number	Diagnoses
1	Osteoarthritis
2	Rheumatoid Arthritis
3	Gouty Arthritis
4	Arthritis – Not OA, RA or Gout
5	Gastrointestinal Perforation, Ulcer and Bleeding
6	Kidney Disease
7	Edema
8	Heart Failure or Left Ventricular Dysfunction
9	Myocardial Infarction
10	Unstable Angina Pectoris
11	Subacute Coronary Heart Disease (Not MI or Unstable Angina)
12	Cerebral Infarction
13	Cerebrovascular Accident Not Otherwise Specified
14	Intracerebral Hemorrhage / Subdural Bleed
15	Transient Ischemic Attack
16	Arterial Embolism / Thrombosis
17	Peripheral Vascular Disease Not Otherwise Specified
18	Hypertension

19	Dyslipidemia
20	Diabetes Mellitus
21	Sudden / Unexplained Death
22	Deep Venous Thrombosis
23	Pulmonary Embolism
24	Ankylosing Spondylitis
25	Intermittent Claudication
26	Acute renal failure / impairment
27	Atherosclerotic CVD