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PASS information

Title	**Etoricoxib Prescribing Patterns and Adverse Events of Interest during Etoricoxib Treatment in UK Primary Care** **Final Study Report 2015**
Version identifier of the final study report	**Version 7 Final Report** **[i.e. the 6th update of the original report of 26 January 2007]**
Date of last version of the final study report	**23November2015**
EU PAS register number	**This study is not so registered**
Active substance	**Etoricoxib** **ATC Code: M01AH05**
Medicinal product	**Arcoxia (etoricoxib)**
Product reference	**CHMP/438258/08**
Procedure number	**EMEA/438258/2008**
Marketing authorisation holder(s)	**Merck Sharp & Dohme Corp.**
Joint PASS	**No**
Research question and objectives	**What are the characteristics of patients prescribed etoricoxib and what are the prescribing patterns of etoricoxib by general practitioners (GPs) in the UK? What are the absolute incidence rates of adverse events (AEs) among patients prescribed etoricoxib in the UK?** **The specific objectives 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 Clinical Practice Research Datalink (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.**
Key results and conclusion	**Etoricoxib is, in general, appropriately prescribed to patients with labeled indications for etoricoxib therapy based on available diagnostic data in CPRD.** **A large proportion of patients prescribed etoricoxib do not have a recorded explicit diagnosis for a labeled indication for etoricoxib in the medical record. Note that the fact that no specific terms were recorded for one of the labelled indications does not necessarily mean that patients were treated 'off label'. For example, many GP's may record a less-specific diagnosis such as "knee pain", which could well be OA or RA but not recorded as such. Such less-specific diagnoses are often consistent with one or more of the diagnoses for a labeled indication, and therefore, it is difficult to estimate the proportion of patients treated without one of the labeled indications. Moreover, patients may be diagnosed by specialists in secondary care but prescribed etoricoxib by their GPs in primary care. Thus, in the CPRD, we see a prescription for etoricoxib recorded by GPs, but because records from secondary care are not included in the CPRD, we do not see diagnoses (possibly for a labeled indication) which may be associated with an etoricoxib prescription recorded by specialists.**

	The baseline characteristics of the population are as expected given the indications for therapy, including the common occurrence of risk factors for both Gastrointestinal (GI) and Cardiovascular (CV) clinical events. **Given the characteristics of the patient population, the safety profile of etoricoxib in general clinical practice is consistent with the safety profile of the product as previously demonstrated during clinical development and through post-marketing pharmacovigilance and as reflected in the SmPC. Overall, the results of this study do not change the previously established favourable risk profile for etoricoxib.**
Country(-ies) of study	**United Kingdom**
Author	PPD **Merck** **UG1D-60** **PO Box 1000** **North Wales, PA 19454-1099** PPD **Merck** **UG1D-60** **PO Box 1000** **North Wales, PA 19454-1099** PPD

Marketing authorisation holder(s)

Marketing authorisation holder(s)	**Merck Sharp & Dohme Corp.,** **A subsidiary of Merck & Co., Inc.** **Whitehouse Station, NJ, USA**
MAH contact person	PPD

Final Study Report
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ISAC Protocol Number: 06_008

Etoricoxib Prescribing Patterns and Adverse Events of Interest during Etoricoxib Treatment in UK Primary Care

PPD

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Merck Sharp & Dohme Corp.,

A subsidiary of Merck & Co., Inc.

Whitehouse Station, NJ, USA

26 January 2007

Updated 18 November 2007

Updated 31 March 2010

Updated 5 May 2011

Updated 24 April 2012

Updated 25 April 2013

Updated 18 June 2014

Updated 23 November 2015

Table Of Contents

List of Tables

List of Figures

1. Abstract

Title

Etoricoxib Prescribing Patterns and Adverse Events of Interest during Etoricoxib Treatment in UK Primary Care -- Final Report, 23 November 2015

PPD

Merck Sharp & Dohme Corp.

Keywords

Arcoxia, etoricoxib, osteoarthritis, rheumatoid arthritis, gouty arthritis, ankylosing spondylitis, arthritis, Clinical Practice Research Datalink, observational database analysis

Rationale and background

This report describes the seventh updated analysis / final results of a June 2005 post-authorization commitment to the European Medicines Agency (EMA). This update further extends the study period to 30 June 2014.

Research question and objectives

To evaluate characteristics of patients prescribed etoricoxib, patterns in the prescribing of etoricoxib by general practitioners (GPs), and to estimate the absolute incidence rate of adverse events (AEs) among new users of etoricoxib.

Study design

A retrospective historical cohort study design was used with follow-up period of up to 1 year to descriptively compare prescribing patterns across cohorts. Analyses of AEs of interest were conducted in which etoricoxib exposure status was allowed to vary over the course of follow-up.

Setting

The study population consisted of patients in the United Kingdom (UK) who had at least one outpatient prescription record for etoricoxib issued during the period 1 April 2002 to 30 June 2013. Two calendar-time sub-cohorts, one before and one after the Urgent Safety Restriction, defined by the date the first etoricoxib prescription was written for a given patient were analysed – Sub-cohort 1 (1 April 2002 to 17 February 2005) and Sub-cohort 2 (18 February 2005 to30 June 2013). A third sub-cohort, referred to as "continuing users", defined as patients in Sub-cohort 1 who subsequently received at least one additional etoricoxib prescription after the Urgent Safety Restriction was also analysed (Sub-cohort 3).

Subjects and study size, including dropouts

Over the study period of almost 11 years, 79,189 patients who met the study inclusion and exclusion criteria received an initial prescription for etoricoxib (n=33,255 in Sub-cohort 1 and n=45,934 in Sub-cohort 2). Of these, 8459 were "continuing users" (Sub-cohort 3).

Variables and data sources

The UK Clinical Practice Research Datalink (CPRD) was used, and the AEs of interest included GI, edema, renal impairment / failure, hypertension, heart failure, and vascular events and sudden / unexplained death during periods of assumed etoricoxib treatment.

Results

Approximately 60% of the patients prescribed etoricoxib are female, and the mean age of the study population is about 60 years. Etoricoxib tends to be prescribed to patients with a history of or at risk of GI events and tend to have a history of or be at risk for cardiovascular disease. Primary gastrointestinal clinical events (perforation, ulcers, or bleeding) were uncommon in Sub-cohort 2 whereas new prescriptions for new gastrointestinal medications were common (50.5/1000py). In Sub-cohort 2, new diagnoses of edema were more common (21.2/1000py) while acute renal impairment or failure (2.4/1000py) and congestive heart failure (2.8/1000py) were uncommon. Overall, acute vascular events of any type were common (11.9/1000py), with Coronary Heart Disease at a rate of 2.7/1000py, and cerebrovascular events of any type occurred at a rate of 5.8/1000py. DVT and PE were uncommon, with rates of 3.7 and 1.3/1000py, respectively. Sudden deaths were rare.

Discussion

Etoricoxib is, in general, appropriately prescribed to patients with labelled indications. The baseline characteristics of the population are as expected given the indications for therapy. The incidences of AEs of special interest with use of etoricoxib are as expected for the NSAID class. Among new users without prior events who were first prescribed etoricoxib after the Urgent Safety Restriction and who were followed over a 1-year period, the incidences of potentially more serious clinical events occurred uncommonly. The results of this analysis suggest, given the characteristics of the patient population, the safety profile of etoricoxib in general clinical practice is consistent with the safety profile of the product as previously demonstrated during clinical development and through post-marketing pharmacovigilance and as reflected in the SmPC. Overall, the results of this study do not change the previously established favourable benefit-risk profile for etoricoxib.

Marketing Authorisation Holder (MAH)

Merck Sharp & Dohme Corp.

Names and affiliations of principal investigators

PPD

Merck Sharp & Dohme Corp.

2. List of abbreviations

ACE (inhibitors) = Angiotensin-Converting Enzyme (inhibitors)

Adenoma Prevention with celecoxib Trial = APC (trial)

AEs = Adverse Events

AS = Ankylosing Spondylitis

ATC = Anatomical Therapeutic Chemical (classification codes, World Health Organization)

BHF = British Heart Foundation

BL = baseline

BMI = Body Mass Index

BNF Codes = British National Formulary (codes)

BP = Blood Pressure

CHD = Coronary Heart Disease

CHMP = Committee for Medicinal Products for Human Use (of the EMA)

CI = Confidence Interval

CIOMS = Council for International Organizations of Medical Sciences

COX-2 = Cyclooxygenase-2

Coxib = selective COX-2 inhibitor

CPRD = Clinical Practice Research Datalink

CSM = Committee on the Safety of Medicines (UK)

CV = cardiovascular

DBP = diastolic blood pressure

DCP =Decentralized procedure (for approval)

DDD = defined daily dose

DMARDS = disease-modifying anti-rheumatic drugs

DVT = Deep Venous Thrombosis

EMA = European Medicines Agency

FF-CPRD = Full Feature Clinical Practice Research Datalink (UK)

F/U = follow-up

GI = Gastrointestinal

GPs =General Practitioners

ISAC = Independent Scientific Advisory Committee (UK)

MAH = Marketing Authorization Holder

MEDAL = Multinational Etoricoxib and Diclofenac Arthritis Long-term (Program of studies)

MHRA = Medicines and Healthcare Products Regulatory Agency (UK)

MI = Myocardial Infarction

mm Hg = millimetres of mercury

MPR =medication possession ratio

MSD = Merck, Sharp & Dohme, Inc.

N/A = Not Applicable

NCI = National Cancer Institute (US)

NICE = National Institute for Clinical Excellence (UK)

NOS = Not otherwise specified

NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

NYHA = New York Heart Association

OA = osteoarthritis

OMDB = Oracle One Merck Database

OXMIS = Oxford Medical Information System (code)

PE = Pulmonary Embolism

POMR = problem-oriented medical record

PPI = proton-pump inhibitor

PSUR = Periodic Safety Update Reports

PUB = Upper Gastrointestinal Tract Bleeding [Peptic Ulcer Bleeding]

py = person*years (number of persons multiplied by time per person)

RA = rheumatoid arthritis

SAE = Serious Adverse Event(s)

SBP = systolic blood pressure

SEAG = Scientific and Ethical Advisory Group (of the CPRD)

SPC =Summary of Product Characteristics

TIA = Transient Ischemic Attack

UK = United Kingdom

3. Investigators

The Investigators are PPD

4. Other Responsible Parties

n/a

5. Milestones for the Main/Primary Study

Milestone	Planned date	Actual date	Comments
Start of data collection	*23 MAR 2006*	*23 MAR 2006*	
End of data collection	*31Dec2013*	*30Jun2014*	Added extra follow-up time at request of MHRA for final report
Registration in the EU PAS register	*n/a*	*n/a*	This study is not so registered
Initial report 2007	*26 JAN 2007*	*26 JAN 2007*	
Updated report 2007	*18 NOV 2007*	*18 NOV 2007*	
Update report 2010	*31 MAR 2010*	*31 MAR 2010*	
Updated report 2011	*05 MAY 2011*	*05 MAY 2011*	
Updated report 2012	*24 APR 2012*	*24 APR 2012*	
Updated report 2013	*31 MAR 2013*	*25 APR 2013*	Needed time to re-format report to the recently updated PASS report template.
Updated report 2014	*31 MAY 2014*	*30 JUN 2014*	Needed time to update drug code lists based on significant changes to British National Formulary (BNF)
Final report 2015	*30JUN2015*	*23November 2015*	Decision to provide 2 PASS final reports as part of a Type 2 variation

6. Rationale and 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 study of the CPRD showed that the selective COX-2 inhibitors celecoxib and rofecoxib were preferentially prescribed (i.e. "channelled") 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 labelling 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 labelling 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 report 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 1.5 years to 30 June 2014.

7. Research question and objectives

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.

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.

8. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	*28 FEB 2006*	Misc. sections	Updates made based on ISAC comments	*Per ISAC review*
2	*15 MAY 2006*	Misc. sections	Updates made based on ISAC comments	*Per ISAC review*
3	*31 MAR 2010*	*1. Background* *2. Purpose* *& others*	Redefined 4 calendar time sub-cohorts as two sub-cohorts according to whether a patient's first etoricoxib prescription was before or after the 17 February 2005 Urgent Safety Restriction. Extended the study to 31 December 2008 Added ankylosing spondylitis to list of indications for etoricoxib therapy (new indication since last update) Updated code lists of medications Updated code lists of diagnoses to be current and the same as those used in the AS PASS mentioned	Add more patients and follow-up time to the Analysis Ensure consistency with ankylosing spondylitis post-authorization safety study (AS PASS) currently being conducted by the sponsor using the same database.

Number	Date	Section of study protocol	Amendment or update	Reason
			above. Added paracetamol, TNF inhibitors, and immune suppressants to analyses of baseline medications Added kidney disease, deep venous thrombosis, pulmonary embolism, and atherosclerotic cardiovascular disease as separate medical history variables Clarified that the clinical endpoint renal impairment / failure is intended to be 'acute' events The outcomes of "atrial or ventricular cardiac thrombus" and "subacute coronary heart disease" have been removed from the "acute thromboembolic cardiovascular events" endpoint. The "acute thromboembolic cardiovascular events" endpoint	This change was made to include only major acute coronary events in this endpoint and to be consistent with AS PASS mentioned above.

Number	Date	Section of study protocol	Amendment or update	Reason
			now includes "acute myocardial infarction" and "unstable angina pectoris". Added the endpoints of 'arterial embolism / thrombosis' and 'hypertension diagnosis' (without the requirement for concomitant antihypertensive therapy)	
4	*20 APR 2011*	5. Study Design & 12. Observational Period	Extended the time period for identification of the first etoricoxib prescription for eligible patients by one year to 31 December 2008 Extended the study period (for follow-up of patients) by one year to 31 December 2009	Add more patients to the analysis Add more follow-up time to the analysis
5	*10 APR 2012*	5. Study Design & 12. Observational Period	Extended time period for identification of the first etoricoxib prescription for eligible patients by one year to 31 December 2009 Extended the	Add more patients to the analysis Add more follow-up time to the analysis

Number	Date	Section of study protocol	Amendment or update	Reason
			study period (for follow-up of patients) by one year to 31 December 2010	
6 Addendum for Off-Label Use	*6 AUG 2012*	Separate Protocol document authored & approved	Conduct descriptive analyses of patients prescribed for off-label use of etoricoxib; this includes paediatric patients (i.e. less than age 16 years) & adult patients (i.e. age 16 years or older) in the CPRD GOLD who do not have labelled indications for treatment as pre-specified in the primary study	Determine baseline characteristics of patients prescribed etoricoxib for off-Label Use and how such patients are treated with etoricoxib by GPs in the UK
7	*18 MAR 2013*	5. Study Design & 12. Observational Period List of Appendices	Extended the time period for identification of the first etoricoxib prescription for eligible patients by one year to 31 December 2010 Extended the study period (for follow-up of patients) by one year to 31 December 2011 Updated READ codes for clinical	Add more patients to the analysis Add more follow-up time to the analysis READ codes were last updated in 2007

Number	Date	Section of study protocol	Amendment or update	Reason
			events	
8 Amendment / Addendum for Off-Label Use	*19 MAR 2013*	Separate Protocol document authored & approved	Conduct descriptive analyses of patients prescribed for off-label use of etoricoxib; this includes paediatric patients (i.e. less than age 16 years) & adult patients (i.e. age 16 years or older) in the CPRD GOLD who do not have labelled indications for treatment as pre-specified in the primary study	Determine baseline characteristics of patients prescribed etoricoxib for off-Label Use and how such patients are treated with etoricoxib by GPs in the UK
9	*15 APR 2014*	5. Study Design & 12. Observational Period List of Appendices	Extended the time period for identification of the first etoricoxib prescription for eligible patients by one year to 31 December 2011 Extended the study period (for follow-up of patients) by one year to 31 December 2012 Updated all drug lists	Add more patients to the analysis Add more follow-up time to the analysis Reflect major changes to British National Formulary
10	*01 OCT 2015*	12. Observational Period	Extended the time period for	Add more patients to the

Number	Date	Section of study protocol	Amendment or update	Reason
			identification of the first etoricoxib prescription for eligible patients by 1.5 years to 30 June 2013 Extended the study period (for follow-up of patients) by 1.5 years to 30 June 2014	analysis Add more follow-up time to the analysis
		10	Added analyses to look at high vs. standard doses in OA and RA patients and to look for time trends in baseline characteristics and outcomes.	Analyses requested by MHRA

Comparison of results from updated analyses to those of the original report and first update (2007) should be done very cautiously, for the following reasons:

- Additional indications have been approved since the initial report.
- A significant number of additional patients and follow-up time has been added to each update. 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.
- The diagnosis code lists have been updated, and some endpoints have been redefined; these changes may affect the absolute incidence rates of some clinical outcomes.
- The drug code lists have been updated which may affect the categorization of patients as well as the absolute rates of utilization of some categories of medications (as well as diagnoses when these are based in part on medication use (e.g., diabetes, hypertension).

9. Research methods

9.1. 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 30June 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 (Sub-cohort 3). 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 Full Feature-CPRD (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.

9.2. Setting

Location: United Kingdom

Period of data collection and follow-up: 1 April 2002 to 30 June 2013 with follow-up through 30 June 2014

9.3. Subjects

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:

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.

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

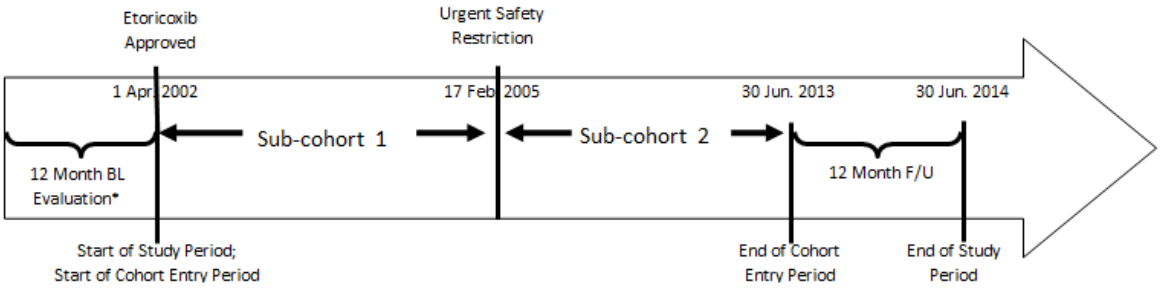
Patient's registration details were not acceptable (i.e., incomplete data on patient's sex, birth year or registration date, or logically implausible dates of death or transferal out of the practice relative to the patients' registration date).

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.

The last date on which a patient could receive a new prescription for etoricoxib and thus enter the cohort for this analysis (30 June 2013) is one year prior to the last date of follow-up for patients in the study (30 June 2014). This allows for a full year of follow-up after the initial prescription of etoricoxib in all patients to facilitate the analysis of the distribution of etoricoxib repeat prescribing over a 1-year period.

The time periods defining the sub-cohorts, relevant dates, the study follow-up period, and other features of the study design are shown graphically in Figure 1.

Figure 1: Sub-cohorts and calendar time



Sub-cohort 3 (Continuing Users) consists of patients in Sub-cohort 1 who received one or more additional etoricoxib prescriptions after the Urgent Safety Restriction

* BL = baseline. The baseline period was 12 months prior to the initial etoricoxib prescription for patients in sub-cohort 1 and 2, and 12 months prior to the first etoricoxib prescription after the Urgent Safety Restriction for patients in Sub-cohort 3

9.4. Variables

Please refer to Protocol Number: 06_008 for details on READ and BNF codes for these variables. Note that READ codes for medical events for this report were updated in 2013 from the original report. A notable increase in number of codes (>20 codes from original report) were found for unstable angina, deep venous thrombosis, kidney disease, hypertension, congestive heart failure, diabetes, edema, and arthritis not AS OA RA gout.

All drug exposures are determined using drug code lists derived from the British National Formulary (BNF). 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. Because of the changes to the drug code lists, the proportion of drugs that have missing dose information has increased since 2013.

9.4.1. Exposure

See note above regarding updates of all exposures.

Primary exposure of interest is etoricoxib.

Other drug exposures of interest:

- Medications for musculoskeletal and joint diseases:
- 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, infliximab, 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 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 from 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:

    - 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 used 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.

9.4.2. Outcomes

- Gastrointestinal Ulcer, Perforation and Bleeding

- Kidney disease

    - Acute Renal Failure / impairment

    - Edema

- Heart failure or Left ventricular dysfunction
- Coronary Heart Disease:
  - Myocardial infarction
  - Unstable angina pectoris
  - Subacute coronary heart disease
- Cerebrovascular Disease:
  - Cerebral infarction
  - Cerebrovascular accident not otherwise specified
  - Intracerebral hemorrhage / subdural bleed
  - Transient ischemic attack
- Peripheral Arterial Disease:
  - Arterial embolism / thrombosis
  - Intermittent claudication
  - Peripheral vascular disease not otherwise specified
  - Deep venous thrombosis
  - Pulmonary embolism
- Atherosclerotic cardiovascular disease
- Hypertension diagnosis
- Dyslipidemia
- Diabetes mellitus

9.4.3. Covariates

- Demographic Variables: gender, age
- Diagnoses:

- Musculoskeletal Disease (inferred indications for etoricoxib use)
  - 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
- Other diagnoses
  - 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
  - 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]

- Cardiovascular medications (categorized by BNF chapter):

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

- Outcomes (occurring during baseline) serving as covariates:
  - 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
- Diabetes mellitus

9.5. Data sources and measurement

The data source for this study is the UK**,** Clinical Practice Research Datalink (CPRD) formerly called the General Practice Research Database (GPRD).

The validity of this data is described in the following CPRD source: http://www.cprd.com/governance/.

9.6. Bias

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.

9.7. Study size

All data analyses were purely descriptive and no statistical hypothesis tests were conducted in this observational study.

9.8. Data transformation

Not applicable.

9.8.1 Data management

We conducted all statistical analyses using SAS version 9.3.1.

9.9. Statistical methods

9.9.1. Main summary measures

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 analysed as categorical variables using the cut-points defined in section 9.4.

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.

9.9.2. Main statistical methods

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 (maximum of 1 year following the date of the index etoricoxib prescription subject to the truncation rules stated above) and the entire available follow-up data. However, descriptive comparisons of events during intended etoricoxib treatment among the sub-cohorts will be made using the (up to) 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.

For the analyses based on the (up to) 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.

In summary, time at risk (exposure) for a given patient is calculated as follows:

- For "First Year Follow-up and First Course Exposure" tables, exposure (patient years) is calculated as the time from the incident drug use date to whichever of the following three came first: the event of interest, end of **first** treatment course, end of **1st year follow-up**.
- For "First Year Follow-up and All Courses Exposure", patients years are calculated as the sum of **all of** the exposed time after the date of dispensing **within the 1st year of follow up**.
- For "Entire Available Follow-up and All Courses Exposure", patient years are calculated as the sum of **all** the exposed time based on dispensing throughout the patient's **entire follow up.**

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 (up to) 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 (up to) 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.

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.

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 four target indications of OA, RA, AS 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. These patients will be subject of the addendum report (Part B) describing patients without one of the labelled indications.

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 or first 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.

9.9.3. Missing values

Patients with missing data on duration of a prescription will be assigned the median value for this parameter for their specific indication.

9.9.4. Sensitivity analyses

Incidence of Clinical Outcomes
For each type of AE, analyses will be done separately in patients with and without a prior medical history of that event.

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.

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.

Repeat Etoricoxib Prescribing

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.

9.9.5. Amendments to the statistical analysis plan

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.

9.10. Quality control

In the CPRD, a patient is deemed "Acceptable" unless any one of the following is true:

1. First registration date or current registration date is missing
2. The birth year is missing
3. The first registration date or current registration date is prior to their birth date
4. The current registration date is prior to the first registration date
5. A transferred out reason but no transferred out date
6. A transferred out date but no transferred out reason
7. A transferred out date prior to their first or current registration date
8. A gender other than Female/Male/Indeterminate
9. Patient is > 115 years (last collection year - birth year), when patient has not transferred out
10. Patient is > 115 years (transfer out year - birth year), when patient has transferred out
11. Patient's records contain events prior to patient's year of birth in the patient's clinical, consultation, immunisation, referral, test or therapy records
12. No permanent registration records
13. All events for the patient have invalid or missing event dates

The Up-To-Standard (UTS) date of a practice is calculated using a combination of gap analysis and assessment of mortality rates, every time a collection from the practice is processed.

Death recording: this takes the practice size into account, and adjusts the number of days between two deaths that is allowable before the practice is deemed not up-to-standard.

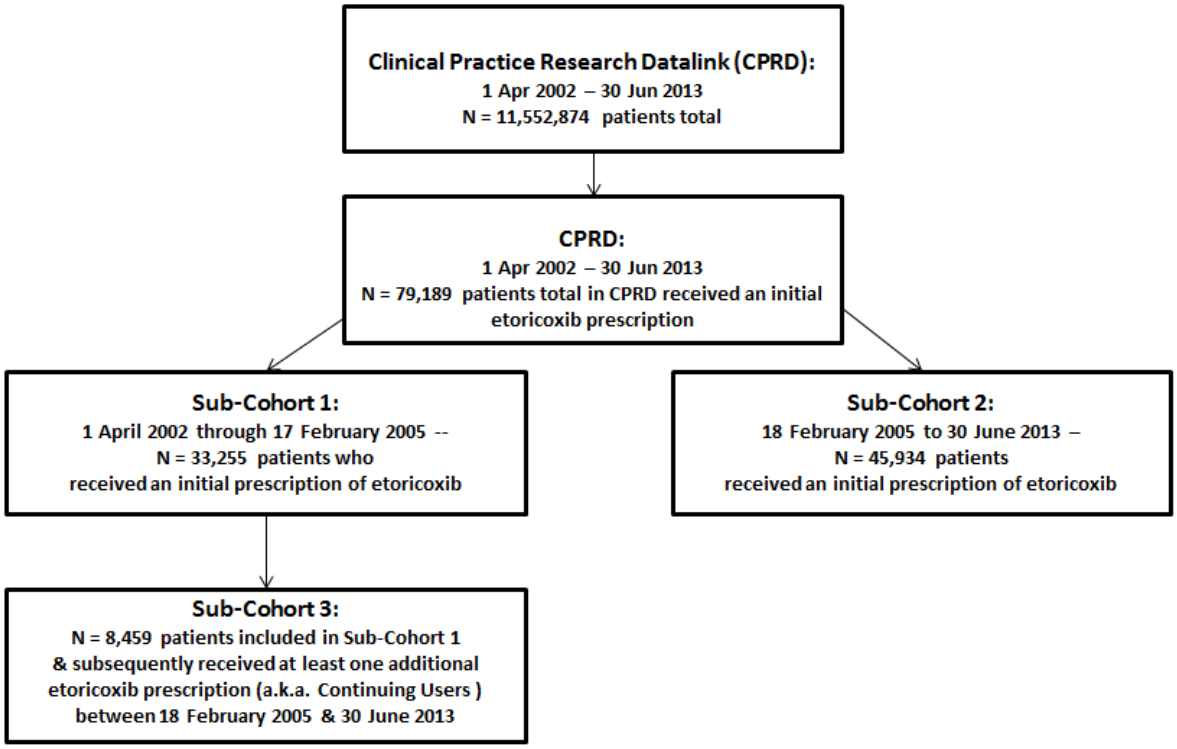
Gap Analysis: A gap date is calculated which is the earliest date after which there are no significant gaps in the data. A sliding window approach is used, meaning there must be 5 consecutive 7-day windows where the number of events in each window falls below 30% of the median. The gap date is calculated for each of the event types (Clinical, Consultation, and Therapy), and is set to be the latest of these. Gaps in Immunisation, Test and Referral data do not affect the UTS date.

10. Results

10.1. Participants

During the period 1 April 2002 through 17 February 2005 (Sub-cohort 1) a total of 33,255 patients received an initial prescription for etoricoxib. This discrepancy from the previous year's report (n=33,960 is due to 1) changes (additions/deletions in practices included in this year's CPRD update vs. the previous year; 2) changes (additions/deletions) in the patients registered with a CPRD-contributing practice in this year's update compared to the previous year's update; 3) patient registration details were not acceptable for this year's update but were for the previous year's update (or vice versa). During the period 18 February 2005 to 30 June 2013 (Sub-cohort 2) a total of 45,934 patients received an initial prescription for etoricoxib. Therefore, over the study period of almost eleven years, 79,189 patients who met the study inclusion and exclusion criteria received an initial prescription for etoricoxib. There were 8459 continuing users of etoricoxib in Sub-cohort 3 (patients who were included in Sub-cohort 1, and who subsequently received at least one additional etoricoxib prescription between 18 February 2005 and 30 June 2013). A patient flow chart showing patient counts in each sub-cohort from the overall CPRD is shown in **Figure 2**.

Figure 2-Patient Flow Chart



The presentation of results will focus on Sub-cohorts 2 and 3, since these both include patients prescribed etoricoxib following the Urgent Safety Restriction.

10.1.1. Protection of Human Subjects

This study uses the UK Clinical Practice Research Datalink. The data that are received by the MAH are de-identified to protect data privacy. No explicit consent is needed for the study because patients are informed that their de-identified healthcare data may be used for research purposes.

10.2. Descriptive data

- **Baseline Characteristics**

For Sub-cohorts 1 and 2, baseline characteristics and demographics were assessed during the 12 months prior to the index etoricoxib prescription. For Sub-cohort 3, they were assessed during the 12 months preceding their first etoricoxib prescription following the Urgent Safety Restriction (not their initial etoricoxib prescription, which would have occurred during the first sub-cohort calendar time period).

- **Indication for Etoricoxib Treatment**

Among Sub-cohort 2 patients, 32% had OA, 3.1% RA, 13.5% Gout, 1.3% AS, 5.5% more than one of the above indications, and 5.2% non-specific Arthritis (**Table 1**). Of note, we were not able to infer, based on the algorithm used, the indication for treatment for 39.4% of the patients in Sub-cohort 2 because the method specified that if none of the diagnoses used for the algorithm were present, the indication was "None of the Above Indications" (indications other than those listed were not specifically sought, but for example these included knee pain, etc.). GPs were not queried as to indication for etoricoxib treatment in such cases. In Sub-cohort 3 (continuing users after 17 February 2005) 44% had OA, 5.6% RA, 12.4% Gout, 1.8% AS, 8.1% more than one of the above indications, and 6.1% non-specific Arthritis. About 22.3% of Sub-cohort 3 had "None of the Above Indications" in their medical record. The addendum to this report, which describes the baseline clinical characteristics among patients prescribed etoricoxib with “None of the Above Indications”, comprises Annex 3, Part B.

- **Demographics**

Sub-cohorts 2 and 3 included 57-59% women and 41-43% men. Patients in Sub-cohort 2 were, on average, 58 years old while those in Sub-cohort 3 were about 62 years old. The proportion of patients ≥65 years was about 34% in Sub-cohort 2 and about 42% in Sub-cohort 3. (**Table 1**)

Analyses stratified by age <65 and ≥65 years are shown in **Tables 1a and 1b**.

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Table 1
Baseline Demographics and Indication for Etoricoxib, by Calendar Time Sub-cohort

Characteristic	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Indication for etoricoxib use n (%)			
Osteoarthritis	13752 (41.35)	14678 (31.95)	3698 (43.72)
Rheumatoid arthritis	1181 (3.55)	1435 (3.12)	475 (5.62)
Gouty arthritis	2877 (8.65)	6205 (13.51)	1047 (12.38)
Ankylosing spondylitis (AS)	286 (0.86)	597 (1.30)	154 (1.82)
More than one OA RA Gout or AS diagnoses	2278 (6.85)	2518 (5.48)	687 (8.12)
Arthritis NOS[#]	1709 (5.14)	2395 (5.21)	513 (6.06)
None of the Above Indications	11172 (33.59)	18106 (39.42)	1885 (22.28)
Gender n (%)			
Male	13136 (39.50)	19748 (42.99)	3437 (40.63)
Female	20119 (60.50)	26185 (57.01)	5022 (59.37)
Indeterminate	0 (0.00)	1 (0.00)	0 (0.00)
Age (years)			
N	33255	45934	8459
Mean	60.70	57.90	62.06
Std. Deviation	15.80	15.91	14.23
Minimum	12.73	2.81	16.12
25th Percentile	49.76	46.52	52.31
Median	61.34	58.16	62.34
75th Percentile	72.81	69.57	72.66
Maximum	104.76	103.63	101.72
Age<65 Years n (%)	19337 (58.15)	30195 (65.74)	4870 (57.57)
Age>=65 Years n (%)	13918 (41.85)	15739 (34.26)	3589 (42.43)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified as OA, RA, AS, or Gout

*For this and subsequent tables “None of the Above Indications" includes indications other than those listed. These were not specifically sought, but these included, for example, knee pain.)

Table 1a
Baseline Demographics and Indication for Etoricoxib, by Calendar Time Sub-cohort
Age < 65 Years

Characteristic	Sub-cohort 1[†] (N=19337)	Sub-cohort 2[‡] (N=30195)	Sub-cohort 3[§] (N=4870)
Indication for etoricoxib use n (%)			
Osteoarthritis	6250 (32.32)	7378 (24.43)	1719 (35.30)
Rheumatoid arthritis	784 (4.05)	1046 (3.46)	334 (6.86)
Gouty arthritis	1518 (7.85)	3634 (12.04)	588 (12.07)
Ankylosing spondylitis (AS)	255 (1.32)	550 (1.82)	142 (2.92)
More than one OA RA Gout or AS diagnoses	984 (5.09)	1048 (3.47)	338 (6.94)
Arthritis NOS[#]	1208 (6.25)	1859 (6.16)	396 (8.13)
None of the Above Indications	8338 (43.12)	14680 (48.62)	1353 (27.78)
Gender n (%)			
Male	8084 (41.81)	13392 (44.35)	2098 (43.08)
Female	11253 (58.19)	16802 (55.64)	2772 (56.92)
Indeterminate	0 (0.00)	1 (0.00)	0 (0.00)
Age (years)			
N	19337	30195	4870
Mean	49.95	48.88	52.26
Std. Deviation	10.81	10.96	9.41
Minimum	12.73	2.81	16.12
25th Percentile	42.65	41.82	46.10
Median	52.20	50.44	54.54
75th Percentile	58.76	57.87	59.78
Maximum	64.99	64.99	64.99

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified as OA, RA, AS, or Gout

Table 1b
Baseline Demographics and Indication for Etoricoxib, by Calendar Time Sub-cohort
Age >= 65 Years

Characteristic	Sub-cohort 1[†] (N=13918)	Sub-cohort 2[‡] (N=15739)	Sub-cohort 3[§] (N=3589)
Indication for etoricoxib use n (%)			
Osteoarthritis	7502 (53.90)	7300 (46.38)	1979 (55.14)
Rheumatoid arthritis	397 (2.85)	389 (2.47)	141 (3.93)
Gouty arthritis	1359 (9.76)	2571 (16.34)	459 (12.79)
Ankylosing spondylitis (AS)	31 (0.22)	47 (0.30)	12 (0.33)
More than one OA RA Gout or AS diagnoses	1294 (9.30)	1470 (9.34)	349 (9.72)
Arthritis NOS[#]	501 (3.60)	536 (3.41)	117 (3.26)
None of the Above Indications	2834 (20.36)	3426 (21.77)	532 (14.82)
Gender n (%)			
Male	5052 (36.30)	6356 (40.38)	1339 (37.31)
Female	8866 (63.70)	9383 (59.62)	2250 (62.69)
Age (years)			
N	13918	15739	3589
Mean	75.63	75.22	75.37
Std. Deviation	7.12	7.19	7.03
Minimum	65.00	65.00	65.00
25th Percentile	69.65	69.13	69.65
Median	74.82	74.11	74.63
75th Percentile	80.59	80.11	80.28
Maximum	104.76	103.63	101.72

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified as OA, RA, AS, or Gout

- **Baseline Cardiovascular Risk Factors**

Baseline cardiovascular risk factors (smoking, body mass index, systolic and diastolic blood pressures) are shown in **Table 2**. For Sub-cohorts 1 and 2, these were assessed during the 12 months prior to the index etoricoxib prescription. For Sub-cohort 3, they were assessed during the 12 months preceding the first etoricoxib prescription following the Urgent Safety Restriction (not the initial etoricoxib prescription, which would have occurred during the first sub-cohort calendar time period). For smoking status, BMI, and blood pressure values, the latest measurement recorded during the baseline period was analysed. It is important to note that the median number of days between the latest baseline blood pressure values in the patient's record and the initial prescription for etoricoxib was 215, 206, and 186 days for Sub-cohorts 1, 2 and 3, respectively. Thus, the baseline blood pressure value for a given patient does not necessarily reflect that patient's blood pressure at the time etoricoxib was initially prescribed.

In Sub-cohort 2, about 27% of patients were ex-smokers, 51% were non-smokers, and 21% were smokers. Mean BMI in this sub-cohort was 28.2 and the median was 27.4. The proportion of patients in Sub-cohort 2 with BMI ≥30 was 29%. Mean and median baseline systolic blood pressure (SBP) were 132 and 130 mmHg, respectively, and mean and median baseline diastolic blood pressures (DBP) were 78 and 80 mmHg, respectively. The mean and median number of blood pressure measurements during the baseline period was 1.8 and 1.0, respectively in Sub-cohort 2.

In Sub-cohort 3, about 27% of patients were ex-smokers, 51% were non-smokers, and 20% were smokers. Mean BMI in this sub-cohort was 28.5 and the median was 27.7. The proportion of patients in Sub-cohort 3 with BMI ≥30 was 30%. Mean and median SBP were both about 136 and mean and median baseline DBP were 79 and 80 mmHg, respectively. The mean and median number of blood pressure measurements during the baseline period was 2.0 and 1.0, respectively in Sub-cohort 3.

Analyses stratified by age <65 and ≥65 years are shown in **Tables 2a and 2b.**

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Table 2
Baseline Cardiovascular Risk Factors by Calendar Time Sub-cohort

Characteristic	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Smoking Status n (%)			
Missing	2605 (7.83)	581 (1.26)	216 (2.55)
Ex-Smoker	7235 (21.76)	12221 (26.61)	2268 (26.81)
Non-Smoker	16129 (48.50)	23457 (51.07)	4316 (51.02)
Smoker	7286 (21.91)	9675 (21.06)	1659 (19.61)
Body Mass Index(kg/m2)			
N	27641	41221	7437
Mean	27.66	28.19	28.50
Std. Deviation	5.38	5.65	5.76
Minimum	15.00	15.00	15.00
25th Percentile	23.90	24.20	24.50
Median	26.90	27.40	27.70
75th Percentile	30.50	31.30	31.50
Maximum	54.00	54.00	53.90
< 20 n (%)	1068 (3.21)	1532 (3.34)	244 (2.88)
20-24 n (%)	8224 (24.73)	11024 (24.00)	1855 (21.93)
25-29 n (%)	10593 (31.85)	15360 (33.44)	2823 (33.37)
>= 30 n (%)	7756 (23.32)	13305 (28.97)	2515 (29.73)
Missing n (%)	5614 (16.88)	4713 (10.26)	1022 (12.08)
Systolic Blood Pressure (mmHg)			
N	31736	44823	8294
Mean	136.05	131.91	135.86
Std. Deviation	18.69	16.22	17.44
Minimum	63.00	70.00	63.00
25th Percentile	121.00	120.00	124.00
Median	136.00	130.00	136.00
75th Percentile	148.00	140.00	145.00
Maximum	266.00	228.00	225.00
< 140 n (%)	16915 (50.86)	29174 (63.51)	4496 (53.15)
140-149 n (%)	7365 (22.15)	10025 (21.82)	2174 (25.70)
150-159 n (%)	3758 (11.30)	3226 (7.02)	854 (10.10)
>= 160 n (%)	3698 (11.12)	2398 (5.22)	770 (9.10)
Missing n (%)	1519 (4.57)	1111 (2.42)	165 (1.95)
Diastolic Blood Pressure (mmHg)			
N	31638	44787	8276
Mean	79.55	78.19	79.39
Std. Deviation	9.71	9.53	9.50
Minimum	40.00	40.00	40.00
25th Percentile	72.00	70.00	73.00
Median	80.00	80.00	80.00
75th Percentile	85.00	84.00	85.00
Maximum	138.00	140.00	146.00
< 90 n (%)	26361 (79.27)	39421 (85.82)	7075 (83.64)
>=90 n (%)	5277 (15.87)	5366 (11.68)	1201 (14.20)
Missing n (%)	1617 (4.86)	1147 (2.50)	183 (2.16)
Number of Blood Pressure Measurements in prior 6 months			

Characteristic	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
N	14469	20676	4086
Mean	1.96	1.82	1.99
Std. Deviation	1.67	1.51	1.76
Minimum	1.00	1.00	1.00
25th Percentile	1.00	1.00	1.00
Median	1.00	1.00	1.00
75th Percentile	2.00	2.00	2.00
Maximum	33.00	28.00	31.00
Missing n (%)	18786 (56.49)	25258 (54.99)	4373 (51.70)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

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Table 2a
Baseline Cardiovascular Risk Factors by Calendar Time Sub-cohort
Age < 65 Years

Characteristic	Sub-cohort 1[†] (N=19337)	Sub-cohort 2[‡] (N=30195)	Sub-cohort 3[§] (N=4870)
Smoking Status n (%)			
Missing	1643 (8.50)	446 (1.48)	125 (2.57)
Ex-Smoker	3473 (17.96)	6704 (22.20)	1106 (22.71)
Non-Smoker	8716 (45.07)	15003 (49.69)	2352 (48.30)
Smoker	5505 (28.47)	8042 (26.63)	1287 (26.43)
Body Mass Index(kg/m2)			
N	15935	26621	4265
Mean	27.83	28.40	28.92
Std. Deviation	5.73	5.95	6.22
Minimum	15.00	15.00	15.00
25th Percentile	23.70	24.10	24.40
Median	26.90	27.50	28.00
75th Percentile	30.90	31.70	32.20
Maximum	54.00	54.00	53.60
< 20 n (%)	679 (3.51)	1033 (3.42)	150 (3.08)
20-24 n (%)	4795 (24.80)	7201 (23.85)	1068 (21.93)
25-29 n (%)	5744 (29.70)	9300 (30.80)	1460 (29.98)
>= 30 n (%)	4717 (24.39)	9087 (30.09)	1587 (32.59)
Missing n (%)	3402 (17.59)	3574 (11.84)	605 (12.42)
Systolic Blood Pressure (mmHg)			
N	18094	29131	4733
Mean	130.79	128.79	131.81
Std. Deviation	17.14	15.66	16.33
Minimum	63.00	70.00	63.00
25th Percentile	120.00	120.00	120.00
Median	130.00	130.00	130.00
75th Percentile	140.00	140.00	140.00
Maximum	266.00	223.00	224.00
< 140 n (%)	11886 (61.47)	21264 (70.42)	3030 (62.22)
140-149 n (%)	3566 (18.44)	5242 (17.36)	1085 (22.28)
150-159 n (%)	1497 (7.74)	1594 (5.28)	358 (7.35)
>= 160 n (%)	1145 (5.92)	1031 (3.41)	260 (5.34)
Missing n (%)	1243 (6.43)	1064 (3.52)	137 (2.81)
Diastolic Blood Pressure (mmHg)			
N	18024	29104	4717
Mean	79.56	78.79	79.95
Std. Deviation	9.80	9.65	9.55
Minimum	40.00	40.00	42.00
25th Percentile	72.00	71.00	74.00
Median	80.00	80.00	80.00
75th Percentile	85.00	85.00	85.00
Maximum	127.00	140.00	146.00
< 90 n (%)	14984 (77.49)	25152 (83.30)	3965 (81.42)
>=90 n (%)	3040 (15.72)	3952 (13.09)	752 (15.44)
Missing n (%)	1313 (6.79)	1091 (3.61)	153 (3.14)

Characteristic	Sub-cohort 1[†] (N=19337)	Sub-cohort 2[‡] (N=30195)	Sub-cohort 3[§] (N=4870)
Number of Blood Pressure Measurements in prior 6 months			
N	6855	11124	1946
Mean	1.80	1.68	1.86
Std. Deviation	1.57	1.36	1.74
Minimum	1.00	1.00	1.00
25th Percentile	1.00	1.00	1.00
Median	1.00	1.00	1.00
75th Percentile	2.00	2.00	2.00
Maximum	33.00	18.00	31.00
Missing n (%)	12482 (64.55)	19071 (63.16)	2924 (60.04)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

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Table 2b
Baseline Cardiovascular Risk Factors by Calendar Time Sub-cohort
Age >= 65 Years

Characteristic	Sub-cohort 1[†] (N=13918)	Sub-cohort 2[‡] (N=15739)	Sub-cohort 3[§] (N=3589)
Smoking Status n (%)			
Missing	962 (6.91)	135 (0.86)	91 (2.54)
Ex-Smoker	3762 (27.03)	5517 (35.05)	1162 (32.38)
Non-Smoker	7413 (53.26)	8454 (53.71)	1964 (54.72)
Smoker	1781 (12.80)	1633 (10.38)	372 (10.37)
Body Mass Index(kg/m2)			
N	11706	14600	3172
Mean	27.43	27.82	27.95
Std. Deviation	4.86	5.05	5.02
Minimum	15.00	15.00	15.20
25th Percentile	24.10	24.40	24.60
Median	26.85	27.20	27.40
75th Percentile	30.10	30.60	30.70
Maximum	54.00	53.60	53.90
< 20 n (%)	389 (2.79)	499 (3.17)	94 (2.62)
20-24 n (%)	3429 (24.64)	3823 (24.29)	787 (21.93)
25-29 n (%)	4849 (34.84)	6060 (38.50)	1363 (37.98)
>= 30 n (%)	3039 (21.84)	4218 (26.80)	928 (25.86)
Missing n (%)	2212 (15.89)	1139 (7.24)	417 (11.62)
Systolic Blood Pressure (mmHg)			
N	13642	15692	3561
Mean	143.02	137.70	141.25
Std. Deviation	18.36	15.66	17.42
Minimum	67.00	75.00	66.00
25th Percentile	130.00	130.00	130.00
Median	140.00	139.00	140.00
75th Percentile	151.00	146.00	150.00
Maximum	247.00	228.00	225.00
< 140 n (%)	5029 (36.13)	7910 (50.26)	1466 (40.85)
140-149 n (%)	3799 (27.30)	4783 (30.39)	1089 (30.34)
150-159 n (%)	2261 (16.25)	1632 (10.37)	496 (13.82)
>= 160 n (%)	2553 (18.34)	1367 (8.69)	510 (14.21)
Missing n (%)	276 (1.98)	47 (0.30)	28 (0.78)
Diastolic Blood Pressure (mmHg)			
N	13614	15683	3559
Mean	79.53	77.08	78.64
Std. Deviation	9.60	9.20	9.39
Minimum	40.00	40.00	40.00
25th Percentile	73.00	70.00	72.00
Median	80.00	79.00	80.00
75th Percentile	85.00	82.00	84.00
Maximum	138.00	130.00	130.00
< 90 n (%)	11377 (81.74)	14269 (90.66)	3110 (86.65)
>=90 n (%)	2237 (16.07)	1414 (8.98)	449 (12.51)
Missing n (%)	304 (2.18)	56 (0.36)	30 (0.84)

Characteristic	Sub-cohort 1[†] (N=13918)	Sub-cohort 2[‡] (N=15739)	Sub-cohort 3[§] (N=3589)
Number of Blood Pressure Measurements in prior 6 months			
N	7614	9552	2140
Mean	2.11	1.98	2.11
Std. Deviation	1.74	1.65	1.78
Minimum	1.00	1.00	1.00
25th Percentile	1.00	1.00	1.00
Median	1.00	1.00	1.00
75th Percentile	3.00	2.00	3.00
Maximum	26.00	28.00	20.00
Missing n (%)	6304 (45.29)	6187 (39.31)	1449 (40.37)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

- **Baseline Medical History**

Baseline medical history by calendar time sub-cohort is described in **Table 3.** For Sub-cohorts 1 and 2, medical history was assessed during the 12 months prior to the index etoricoxib prescription. For Sub-cohort 3, they were assessed during the 12 months preceding the first etoricoxib prescription following the Urgent Safety Restriction (not the initial etoricoxib prescription, which would have occurred during the first sub-cohort calendar time period).

The prevalence of baseline medical conditions was generally similar for Sub-cohorts 2 and 3 except that a history of edema and hypertension were somewhat more common while kidney disease appeared less common in Sub-cohort 3.

Of note, 6-7% of patients in Sub-cohorts 2 and 3 have a history of GI ulcer, bleeding or perforation. About 3-4% have a history of MI, and ~2% a history of stroke. About 31% of Sub-cohort 2 and 37% of Sub-cohort 3 patients have a medical history of hypertension.

Analyses stratified by age <65 and ≥65 years are shown in **Tables 3a and 3b**. As expected, those age ≥65 years have a greater burden of baseline co-morbidity than those younger than 65 years.

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Table 3
Baseline Medical History by Calendar Time Sub-cohort

Medical History	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Gastrointestinal n (%)			
Gastrointestinal Ulcer, Perforation/Bleeding	2218 (6.67)	2779 (6.05)	607 (7.18)
Renovascular n (%)			
Kidney disease	345 (1.04)	3779 (8.23)	342 (4.04)
Acute Renal Impairment/failure	145 (0.44)	275 (0.60)	57 (0.67)
Edema	4524 (13.60)	5794 (12.61)	1362 (16.10)
Congestive Heart Failure n (%)			
Heart failure or Left Ventricular Dysfunction	883 (2.66)	758 (1.65)	174 (2.06)
Cardiac n (%)			
Myocardial Infarction	1516 (4.56)	1544 (3.36)	315 (3.72)
Unstable Angina Pectoris	2899 (8.72)	2538 (5.53)	601 (7.10)
Other (subacute) heart disease	3631 (10.92)	3261 (7.10)	773 (9.14)
Cerebrovascular n (%)			
Intracerebral / Subdural haemorrhage	46 (0.14)	59 (0.13)	9 (0.11)
Cerebral infarction	163 (0.49)	235 (0.51)	43 (0.51)
Cerebrovascular accident NOS[#]	478 (1.44)	522 (1.14)	116 (1.37)
Transient ischemic attack	923 (2.78)	1039 (2.26)	221 (2.61)
Peripheral Arterial Disease n (%)			
Arterial embolism and thrombosis	63 (0.19)	44 (0.10)	13 (0.15)
Intermittent claudication	519 (1.56)	514 (1.12)	133 (1.57)
Peripheral vascular disease NOS[#]	514 (1.55)	473 (1.03)	124 (1.47)
Deep venous thrombosis n (%)			
Deep Venous Thrombosis	1215 (3.65)	1615 (3.52)	332 (3.92)
Pulmonary Embolism n (%)			
Pulmonary Embolism	318 (0.96)	470 (1.02)	77 (0.91)
Hypertension n (%)			
Hypertension	10372 (31.19)	14319 (31.17)	3143 (37.16)
Dyslipidemia n (%)			
Dyslipidemia	3421 (10.29)	5948 (12.95)	1119 (13.23)
Diabetes Mellitus n (%)			
Diabetes diagnostic code	2464 (7.41)	3720 (8.10)	682 (8.06)
Insulin prescription	560 (1.68)	754 (1.64)	130 (1.54)
Oral antidiabetic agent prescription	1527 (4.59)	2506 (5.46)	447 (5.28)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

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Table 3a
Baseline Medical History by Calendar Time Sub-cohort
Age < 65 Years

Medical History	Sub-cohort 1[†] (N=19337)	Sub-cohort 2[‡] (N=30195)	Sub-cohort 3[§] (N=4870)
Gastrointestinal n (%)			
Gastrointestinal Ulcer, Perforation/Bleeding	1043 (5.39)	1401 (4.64)	297 (6.10)
Renovascular n (%)			
Kidney disease	120 (0.62)	910 (3.01)	70 (1.44)
Acute Renal Impairment/failure	28 (0.14)	69 (0.23)	13 (0.27)
Edema	1392 (7.20)	2272 (7.52)	464 (9.53)
Congestive Heart Failure n (%)			
Heart failure or Left Ventricular Dysfunction	75 (0.39)	96 (0.32)	15 (0.31)
Cardiac n (%)			
Myocardial Infarction	324 (1.68)	362 (1.20)	72 (1.48)
Unstable Angina Pectoris	747 (3.86)	627 (2.08)	142 (2.92)
Other (subacute) heart disease	933 (4.82)	804 (2.66)	191 (3.92)
Cerebrovascular n (%)			
Intracerebral / Subdural haemorrhage	12 (0.06)	14 (0.05)	3 (0.06)
Cerebral infarction	37 (0.19)	65 (0.22)	8 (0.16)
Cerebrovascular accident NOS[#]	104 (0.54)	114 (0.38)	23 (0.47)
Transient ischemic attack	165 (0.85)	220 (0.73)	42 (0.86)
Peripheral Arterial Disease n (%)			
Arterial embolism and thrombosis	26 (0.13)	16 (0.05)	4 (0.08)
Intermittent claudication	96 (0.50)	91 (0.30)	32 (0.66)
Peripheral vascular disease NOS[#]	111 (0.57)	115 (0.38)	34 (0.70)
Deep venous thrombosis n (%)			
Deep Venous Thrombosis	474 (2.45)	741 (2.45)	142 (2.92)
Pulmonary Embolism n (%)			
Pulmonary Embolism	131 (0.68)	194 (0.64)	38 (0.78)
Hypertension n (%)			
Hypertension	3596 (18.60)	5683 (18.82)	1213 (24.91)
Dyslipidemia n (%)			
Dyslipidemia	1418 (7.33)	2562 (8.48)	490 (10.06)
Diabetes Mellitus n (%)			
Diabetes diagnostic code	984 (5.09)	1684 (5.58)	299 (6.14)
Insulin prescription	309 (1.60)	432 (1.43)	74 (1.52)
Oral antidiabetic agent prescription	591 (3.06)	1148 (3.80)	193 (3.96)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

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Table 3b
Baseline Medical History by Calendar Time Sub-cohort
Age >= 65 Years

Medical History	Sub-cohort 1[†] (N=13918)	Sub-cohort 2[‡] (N=15739)	Sub-cohort 3[§] (N=3589)
Gastrointestinal n (%)			
Gastrointestinal Ulcer, Perforation/Bleeding	1175 (8.44)	1378 (8.76)	310 (8.64)
Renovascular n (%)			
Kidney disease	225 (1.62)	2869 (18.23)	272 (7.58)
Acute Renal Impairment/failure	117 (0.84)	206 (1.31)	44 (1.23)
Edema	3132 (22.50)	3522 (22.38)	898 (25.02)
Congestive Heart Failure n (%)			
Heart failure or Left Ventricular Dysfunction	808 (5.81)	662 (4.21)	159 (4.43)
Cardiac n (%)			
Myocardial Infarction	1192 (8.56)	1182 (7.51)	243 (6.77)
Unstable Angina Pectoris	2152 (15.46)	1911 (12.14)	459 (12.79)
Other (subacute) heart disease	2698 (19.38)	2457 (15.61)	582 (16.22)
Cerebrovascular n (%)			
Intracerebral / Subdural haemorrhage	34 (0.24)	45 (0.29)	6 (0.17)
Cerebral infarction	126 (0.91)	170 (1.08)	35 (0.98)
Cerebrovascular accident NOS[#]	374 (2.69)	408 (2.59)	93 (2.59)
Transient ischemic attack	758 (5.45)	819 (5.20)	179 (4.99)
Peripheral Arterial Disease n (%)			
Arterial embolism and thrombosis	37 (0.27)	28 (0.18)	9 (0.25)
Intermittent claudication	423 (3.04)	423 (2.69)	101 (2.81)
Peripheral vascular disease NOS[#]	403 (2.90)	358 (2.27)	90 (2.51)
Deep venous thrombosis n (%)			
Deep Venous Thrombosis	741 (5.32)	874 (5.55)	190 (5.29)
Pulmonary Embolism n (%)			
Pulmonary Embolism	187 (1.34)	276 (1.75)	39 (1.09)
Hypertension n (%)			
Hypertension	6776 (48.69)	8636 (54.87)	1930 (53.78)
Dyslipidemia n (%)			
Dyslipidemia	2003 (14.39)	3386 (21.51)	629 (17.53)
Diabetes Mellitus n (%)			
Diabetes diagnostic code	1480 (10.63)	2036 (12.94)	383 (10.67)
Insulin prescription	251 (1.80)	322 (2.05)	56 (1.56)
Oral antidiabetic agent prescription	936 (6.73)	1358 (8.63)	254 (7.08)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

Baseline Medications

The numbers and proportions of patients using various medications at baseline, other than etoricoxib, are shown in **Table 4**. For Sub-cohorts 1 and 2, baseline medications were assessed during the 12 months prior to the index etoricoxib prescription. For Sub-cohort 3, they were assessed during the 12 months preceding the first etoricoxib prescription following the Urgent Safety Restriction (not the initial etoricoxib prescription, which would have occurred during the first sub-cohort calendar time period).

Among patients in Sub-cohort 2, a baseline history of use of coxibs other than etoricoxib was seen in 5.5*%,* use of other NSAIDs regarded as COX-2 selective in 6.6%, use of non-selective NSAIDs in 45.3% and use of paracetamol in 46.2%. Sub-cohort 2 patients had a 3.8% baseline prevalence of H2-receptor antagonist use, and a 34.6% baseline prevalence of PPI use.

Among patients in Sub-cohort 3, a baseline history of use of coxibs other than etoricoxib was seen in 21.4%, use of other NSAIDs regarded as COX-2 selective in 7.1%, use of non-selective NSAIDs in 29.6% and use of paracetamol in 56.3%. Sub-cohort 3 patients also had a 6.3% baseline prevalence of baseline H2-receptor antagonist use, and a 35.2% prevalence of baseline PPI use.

The high prevalence of prior paracetamol (acetaminophen) use in both Sub-cohorts 2 and 3 could reflect their underlying risk of GI events or greater intolerance for non-selective NSAIDs or use of a pain medication prior to or along with non-selective NSAIDs.

There was considerable use of cardiovascular medications at baseline among the patients prescribed etoricoxib, reflecting the prevalence of baseline history of cardiovascular disease, hypertension and dyslipidemia in the study population. The prevalence of baseline use of these medications in Sub-cohort 3 was somewhat greater than that for Sub-cohort 2 which may be in part due to their slightly older age.

Baseline medication history in those age <65 years and in those age ≥65 years are shown in **Tables 4a and 4b.** Compared with those age < 65 years, those age ≥65 years less frequently used non-selective NSAIDs and more frequently used paracetamol during the baseline period. Older patients also more frequently used GI and CV medications during the baseline period consistent with their higher rates of GI and CV comorbidities.

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Table 4
Baseline Medications, by Calendar Time Sub-cohort

Medication	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Musculoskeletal and Joint Diseases n (%)			
Other Coxibs	9620 (28.93)	2530 (5.51)	1809 (21.39)
Other NSAIDs regarded as Cox-2 selective	1954 (5.88)	3009 (6.55)	603 (7.13)
Non-selective NSAIDs	12484 (37.54)	20813 (45.31)	2500 (29.55)
Aspirin	359 (1.08)	182 (0.40)	71 (0.84)
Paracetamol	16312 (49.05)	21241 (46.24)	4766 (56.34)
DMARDS	1287 (3.87)	1643 (3.58)	653 (7.72)
Gout medications	1111 (3.34)	1966 (4.28)	450 (5.32)
Oral Corticosteroids	2559 (7.70)	3972 (8.65)	789 (9.33)
Local Corticosteroids	1380 (4.15)	2314 (5.04)	404 (4.78)
Gastrointestinal Medications n (%)			
Antacids	298 (0.90)	264 (0.57)	69 (0.82)
H2-receptor antagonists	2358 (7.09)	1781 (3.88)	531 (6.28)
Prostaglandin analogues	1386 (4.17)	1802 (3.92)	293 (3.46)
Proton pump inhibitors	8022 (24.12)	15905 (34.63)	2977 (35.19)
Cardiovascular Medications n (%)			
Cardiac glycosides	469 (1.41)	446 (0.97)	111 (1.31)
Diuretics	6026 (18.12)	6674 (14.53)	1678 (19.84)
Beta Blocker	5523 (16.61)	6432 (14.00)	1545 (18.26)
ACE inhibitors	4265 (12.83)	6807 (14.82)	1318 (15.58)
Angiotensin-II receptor	1902 (5.72)	3718 (8.09)	746 (8.82)
Nitrates	2438 (7.33)	2120 (4.62)	536 (6.34)
Calcium-channel blockers	4362 (13.12)	5947 (12.95)	1328 (15.70)
Oral Anticoagulants	484 (1.46)	663 (1.44)	134 (1.58)
Oral antiplatelet drugs	6120 (18.40)	7323 (15.94)	1622 (19.17)
Anion-exchange resins	40 (0.12)	65 (0.14)	14 (0.17)
Ezetimibe	59 (0.18)	779 (1.70)	100 (1.18)
Fibrates	255 (0.77)	318 (0.69)	68 (0.80)
Statins	5414 (16.28)	10457 (22.77)	1903 (22.50)
Nicotinic acid	4 (0.01)	22 (0.05)	2 (0.02)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

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Table 4a
Baseline Medications, by Calendar Time Sub-cohort
Age < 65 Years

Medication	Sub-cohort 1[†] (N=19337)	Sub-cohort 2[‡] (N=30195)	Sub-cohort 3[§] (N=4870)
Musculoskeletal and Joint Diseases n (%)			
Other Coxibs	4973 (25.72)	1473 (4.88)	997 (20.47)
Other NSAIDs regarded as Cox-2 selective	1074 (5.55)	1915 (6.34)	354 (7.27)
Non-selective NSAIDs	7845 (40.57)	14562 (48.23)	1528 (31.38)
Aspirin	104 (0.54)	75 (0.25)	20 (0.41)
Paracetamol	7984 (41.29)	12140 (40.21)	2457 (50.45)
DMARDS	890 (4.60)	1184 (3.92)	479 (9.84)
Gout medications	538 (2.78)	1025 (3.39)	245 (5.03)
Oral Corticosteroids	1189 (6.15)	2196 (7.27)	430 (8.83)
Local Corticosteroids	751 (3.88)	1319 (4.37)	214 (4.39)
Gastrointestinal Medications n (%)			
Antacids	106 (0.55)	119 (0.39)	26 (0.53)
H2-receptor antagonists	1203 (6.22)	989 (3.28)	279 (5.73)
Prostaglandin analogues	704 (3.64)	1047 (3.47)	142 (2.92)
Proton pump inhibitors	4195 (21.69)	9315 (30.85)	1574 (32.32)
Cardiovascular Medications n (%)			
Cardiac glycosides	32 (0.17)	50 (0.17)	7 (0.14)
Diuretics	1954 (10.10)	2357 (7.81)	612 (12.57)
Beta Blocker	2336 (12.08)	2857 (9.46)	691 (14.19)
ACE inhibitors	1420 (7.34)	2757 (9.13)	502 (10.31)
Angiotensin-II receptor	619 (3.20)	1371 (4.54)	272 (5.59)
Nitrates	693 (3.58)	603 (2.00)	164 (3.37)
Calcium-channel blockers	1326 (6.86)	2081 (6.89)	453 (9.30)
Oral Anticoagulants	104 (0.54)	179 (0.59)	26 (0.53)
Oral antiplatelet drugs	1485 (7.68)	2048 (6.78)	441 (9.06)
Anion-exchange resins	16 (0.08)	34 (0.11)	8 (0.16)
Ezetimibe	19 (0.10)	338 (1.12)	39 (0.80)
Fibrates	111 (0.57)	151 (0.50)	30 (0.62)
Statins	1915 (9.90)	4103 (13.59)	714 (14.66)
Nicotinic acid	3 (0.02)	10 (0.03)	1 (0.02)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

Table 4b
Baseline Medications, by Calendar Time Sub-cohort
Age >= 65 Years

Medication	Sub-cohort 1[†] (N=13918)	Sub-cohort 2[‡] (N=15739)	Sub-cohort 3[§] (N=3589)
Musculoskeletal and Joint Diseases n (%)			
Other Coxibs	4647 (33.39)	1057 (6.72)	812 (22.62)
Other NSAIDs regarded as Cox-2 selective	880 (6.32)	1094 (6.95)	249 (6.94)
Non-selective NSAIDs	4639 (33.33)	6251 (39.72)	972 (27.08)
Aspirin	255 (1.83)	107 (0.68)	51 (1.42)
Paracetamol	8328 (59.84)	9101 (57.82)	2309 (64.34)
DMARDS	397 (2.85)	459 (2.92)	174 (4.85)
Gout medications	573 (4.12)	941 (5.98)	205 (5.71)
Oral Corticosteroids	1370 (9.84)	1776 (11.28)	359 (10.00)
Local Corticosteroids	629 (4.52)	995 (6.32)	190 (5.29)
Gastrointestinal Medications n (%)			
Antacids	192 (1.38)	145 (0.92)	43 (1.20)
H2-receptor antagonists	1155 (8.30)	792 (5.03)	252 (7.02)
Prostaglandin analogues	682 (4.90)	755 (4.80)	151 (4.21)
Proton pump inhibitors	3827 (27.50)	6590 (41.87)	1403 (39.09)
Cardiovascular Medications n (%)			
Cardiac glycosides	437 (3.14)	396 (2.52)	104 (2.90)
Diuretics	4072 (29.26)	4317 (27.43)	1066 (29.70)
Beta Blocker	3187 (22.90)	3575 (22.71)	854 (23.79)
ACE inhibitors	2845 (20.44)	4050 (25.73)	816 (22.74)
Angiotensin-II receptor	1283 (9.22)	2347 (14.91)	474 (13.21)
Nitrates	1745 (12.54)	1517 (9.64)	372 (10.37)
Calcium-channel blockers	3036 (21.81)	3866 (24.56)	875 (24.38)
Oral Anticoagulants	380 (2.73)	484 (3.08)	108 (3.01)
Oral antiplatelet drugs	4635 (33.30)	5275 (33.52)	1181 (32.91)
Anion-exchange resins	24 (0.17)	31 (0.20)	6 (0.17)
Ezetimibe	40 (0.29)	441 (2.80)	61 (1.70)
Fibrates	144 (1.03)	167 (1.06)	38 (1.06)
Statins	3499 (25.14)	6354 (40.37)	1189 (33.13)
Nicotinic acid	1 (0.01)	12 (0.08)	1 (0.03)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

10.3. Outcome data

Non-clinical Outcomes

As described in 9.9.3. Missing values, patients with missing data on duration of a prescription were assigned the median value for this parameter for all patients with the same indication for treatment. The numbers (%) of patients with missing data are as follows:

Missing Data

	Sub-cohort 1† (N=33255) n (%)	Sub-cohort 2‡ (N=45934) n (%)
Missing dosage: Any etoricoxib prescriptions during all follow-up time	3955 (11.89)	6552 (14.26)
Missing dosage: Any etoricoxib prescriptions during first year follow-up	3061 (9.20)	5548 (12.08)
Missing dosage: First etoricoxib prescription / course in the first year follow-up	2641 (7.94)	4986 (10.85)
Missing duration: Any etoricoxib prescriptions during all follow-up time	5337 (16.05)	15312 (33.33)
Missing duration: Any etoricoxib prescriptions during first year follow-up	3403 (10.23)	11255 (24.50)
Missing duration: First etoricoxib prescription / course in the first year follow-up	2968 (8.92)	10418 (22.68)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005
‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

The number (%) of patients with only one etoricoxib prescription during the study period is 14,310 (43.0%) for Sub-cohort 1 and 23,096 (50.3%) for Sub-cohort 2.

Initial Etoricoxib Dosing

The distribution of initial etoricoxib dose, by age and calendar time sub-cohort, is shown in **Table 5**. For Sub-cohorts 1 and 2 the initial dose assessment pertains to the initial etoricoxib prescription before and after the Urgent Safety Restriction, respectively. For Sub-cohort 3, it pertains to the first etoricoxib prescription following the Urgent Safety Restriction (not the initial etoricoxib prescription, which would have occurred during the first sub-cohort calendar time period).

Initial etoricoxib doses of 30, 60, 90, and 120mg occurred in 9.7%, 43.2%, 28.4%, and 18.8% of patients initially prescribed etoricoxib after the Urgent Safety Restriction (Sub-cohort 2). In Sub-cohort 3, doses of 30, 60, 90, and 120mg for the first etoricoxib prescription after the Urgent Safety Restriction were observed in 2.1%, 49.0%, 34.3%, and 14.6% of patients.

In both Sub-cohorts 2 and 3, patients aged ≥65 years were more likely to have been prescribed 30 and 60 mg and less likely to have been prescribed 90 and 120 mg doses compared with younger patients.

Table 5
Distribution of Initial Etoricoxib Dose by Age and Calendar Time Sub-cohort

Initial Etoricoxib Dose	Sub-cohort 1† (N=33255)	Sub-cohort 2‡ (N=45934)	Sub-cohort 3§ (N=8459)
All Ages			
N	33255	45934	8459
30 mg	0 (0.00)	4437 (9.66)	176 (2.08)
60 mg	18787 (56.49)	19837 (43.19)	4142 (48.97)
90 mg	9165 (27.56)	13027 (28.36)	2905 (34.34)
120 mg	5303 (15.95)	8633 (18.79)	1236 (14.61)
Age < 65			
N	19337	30195	4870
30 mg	0 (0.00)	2598 (8.60)	86 (1.77)
60 mg	9992 (51.67)	12522 (41.47)	2133 (43.80)
90 mg	5835 (30.18)	9316 (30.85)	1869 (38.38)
120 mg	3510 (18.15)	5759 (19.07)	782 (16.06)
Age >= 65			
N	13918	15739	3589
30 mg	0 (0.00)	1839 (11.68)	90 (2.51)
60 mg	8795 (63.19)	7315 (46.48)	2009 (55.98)
90 mg	3330 (23.93)	3711 (23.58)	1036 (28.87)
120 mg	1793 (12.88)	2874 (18.26)	454 (12.65)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

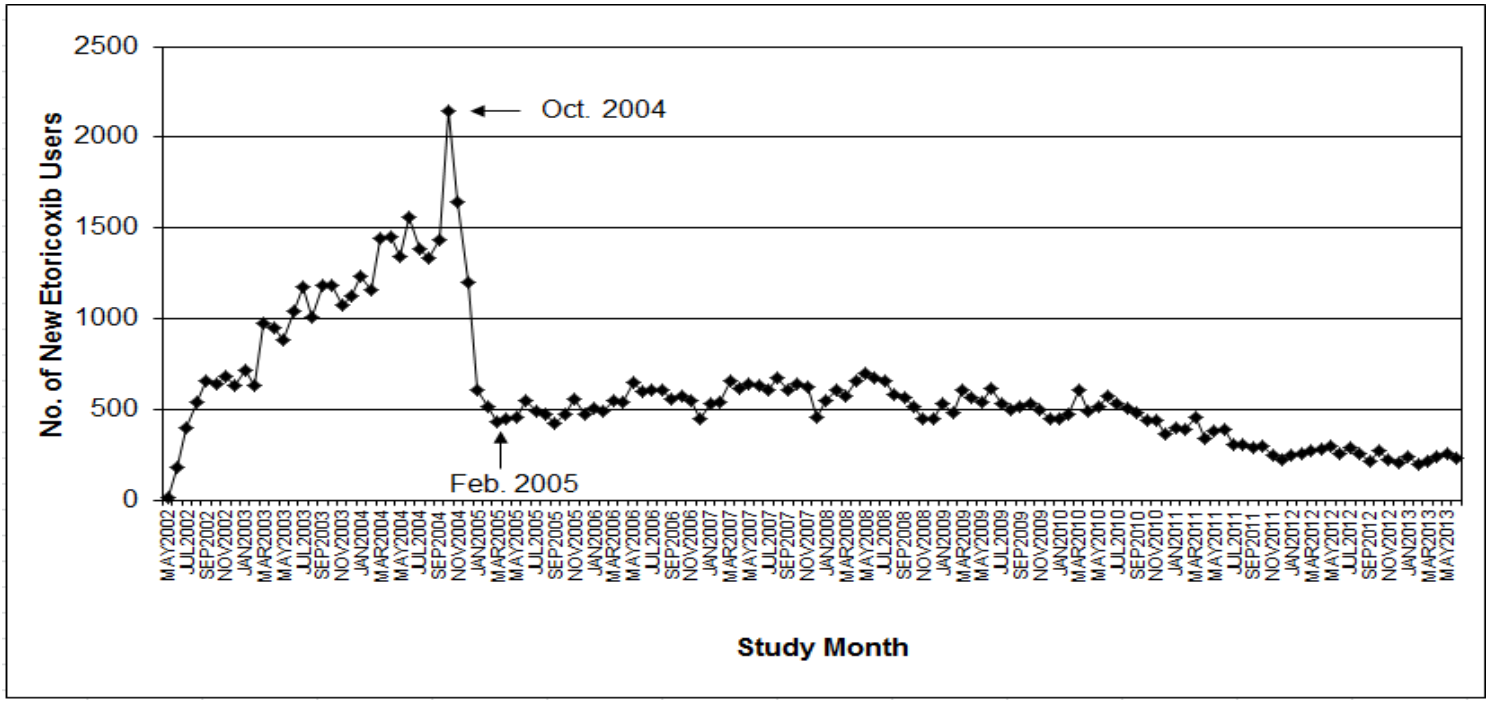
‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

§ First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

New etoricoxib users

The number of new etoricoxib users per study month is shown graphically in **Figure 3**. Since the introduction of etoricoxib in the UK, the number of new users increased steadily through September 2004; the number increased dramatically in October 2004 to a little over 2000 / month. In the following months, until just after the Urgent Safety Restriction in February 2005, the number of new users fell quickly to the lowest level since the fourth month following the introduction of the drug in the UK. Thereafter the new user rate has remained low, between about 400 and 600 per month, with a further decrease to between 300 and 400 new users per month over the last three months of 2010 and to 250 to 300 new users per month in 2011. In 2011, the number of new users per month decreased further with 220-300 new users per month since July 2011.

Figure 3
Rate of New Etoricoxib Users Per Month During the Study Period



The distribution of initial etoricoxib dose by indication is shown in **Table 6**. For Sub-cohorts 1 and 2 the initial dose assessment pertains to the initial etoricoxib prescription before and after the Urgent Safety Restriction, respectively. For Sub-cohort 3, it pertains to the first etoricoxib prescription following the Urgent Safety Restriction (not the initial etoricoxib prescription, which would have occurred during the first sub-cohort calendar time period).

In both Sub-cohorts 2 and 3, among patients with OA only, those with more than one labelled indication, and those with Arthritis NOS, the most commonly prescribed initial dose of etoricoxib was 60 mg, followed by 90 mg. [Note: The 30 mg dose of etoricoxib for OA was approved via DCP in August 2007; this formulation was introduced in late 2007; hence the 30 mg dose had been available for only 6 years of the cohort entry period used in this update]. In Sub-cohorts 2 and 3, among patients with RA only and AS only, the most commonly prescribed initial dose of etoricoxib was 90 mg, followed by 60 mg; among patients with Gout only, the most commonly prescribed initial dose of etoricoxib was 120 mg. Patients in both Sub-cohorts 2 and 3 with none of the above labelled indications for etoricoxib were most frequently prescribed 60 mg, followed by 90 mg.

Table 6
Distribution of Initial Etoricoxib Dose by Indication

Indication	Sub-cohort 1[†] (N=33255) n (%)	Sub-cohort 2[‡] (N=45934) n (%)	Sub-cohort 3[§] (N=8459) n (%)
Osteoarthritis (OA)			
30 mg	0 (0.00)	1827 (12.45)	102 (2.76)
60 mg	8822 (64.15)	7668 (52.24)	2128 (57.54)
90 mg	3616 (26.29)	3966 (27.02)	1176 (31.80)
120 mg	1314 (9.55)	1217 (8.29)	292 (7.90)
Rheumatoid Arthritis (RA)			
30 mg	0 (0.00)	109 (7.60)	5 (1.05)
60 mg	480 (40.64)	488 (34.01)	157 (33.05)
90 mg	604 (51.14)	709 (49.41)	270 (56.84)
120 mg	97 (8.21)	129 (8.99)	43 (9.05)
Gout			
30 mg	0 (0.00)	195 (3.14)	7 (0.67)
60 mg	941 (32.71)	1191 (19.19)	309 (29.51)
90 mg	462 (16.06)	869 (14.00)	189 (18.05)
120 mg	1474 (51.23)	3950 (63.66)	542 (51.77)
Ankylosing spondylitis (AS)			
30 mg	0 (0.00)	31 (5.19)	3 (1.95)
60 mg	108 (37.76)	161 (26.97)	42 (27.27)
90 mg	143 (50.00)	365 (61.14)	91 (59.09)
120 mg	35 (12.24)	40 (6.70)	18 (11.69)
More than one OA RA Gout or AS diagnoses			
30 mg	0 (0.00)	248 (9.85)	7 (1.02)
60 mg	1222 (53.64)	1012 (40.19)	308 (44.83)
90 mg	703 (30.86)	762 (30.26)	281 (40.90)
120 mg	353 (15.50)	496 (19.70)	91 (13.25)
Arthritis NOS[#]			
30 mg	0 (0.00)	222 (9.27)	11 (2.14)
60 mg	944 (55.24)	1068 (44.59)	252 (49.12)
90 mg	572 (33.47)	860 (35.91)	207 (40.35)
120 mg	193 (11.29)	245 (10.23)	43 (8.38)
None of the Above Indications			
30 mg	0 (0.00)	1805 (9.97)	41 (2.18)
60 mg	6270 (56.12)	8249 (45.56)	946 (50.19)
90 mg	3065 (27.43)	5496 (30.35)	691 (36.66)
120 mg	1837 (16.44)	2556 (14.12)	207 (10.98)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

Duration of Etoricoxib Prescribing

For Sub-cohorts 1 and 2, the duration of etoricoxib prescribing pertains to the initial etoricoxib prescription before and after the Urgent Safety Restriction, respectively. For Sub-cohort 3, it pertains to the first etoricoxib prescription following the Urgent Safety Restriction (not the initial etoricoxib prescription, which would have occurred during the first sub-cohort calendar time period).

The median number of days of etoricoxib treatment by indication for the calendar-time sub-cohorts is shown in **Table 7**. Median values are shown because the distribution is highly skewed for many indications, with mean values being much higher than the median values. This analysis includes only those patients who did not later switch to a different dose of etoricoxib. Patients with missing values for duration of prescription were imputed to have the median value for their indication group. All univariate statistics regarding the number of days of etoricoxib treatment by indication are shown in **Table 7a.**

In Sub-cohort 2 over a 1-year period of follow-up, patients with OA were prescribed etoricoxib for a median of 42 days, and patients with Arthritis NOS were prescribed etoricoxib for a median of 56 days. Those with RA and AS were prescribed the drug for a median of 84 and 127days, respectively. Those with Gout, those with more than one indication for etoricoxib, and those without a labelled indication for etoricoxib were prescribed the drug for a median of 21 to 28 days.

Continuing users after the Urgent Safety Restriction (Sub-cohort 3) used etoricoxib for a greater number of days than did patients in Sub-cohort 2 for all indications as might be expected if these patients generally had more severe disease than the other sub-cohorts and/or had tolerated the medication over time.

Similar analyses of the number of days of etoricoxib treatment (all indications combined) by sub-cohort were repeated with exclusion of:

- Patients with imputed values for duration of therapy (**Table 7b** in **Annex 3, Part A)**
- Patients who switched to other NSAIDs (**Table 7c** in **Annex 3, Part A)**

The above analyses were also repeated (all indications combined) using all available follow-up time. (**Table 7d** in **Annex 3, Part A**)

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Table 7
Etoricoxib Prescribing over a 1-year Period of Follow-up
Median Number of Therapy Days, by Inferred Indication

Inferred Indication	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Osteoarthritis (OA)	56.00	42.00	112.00
Rheumatoid arthritis (RA)	112.00	84.00	213.00
Gout	28.00	21.00	28.00
Ankylosing spondylitis (AS)	166.00	127.00	196.00
More than one OA RA Gout or AS diagnoses	56.00	28.00	112.00
Arthritis NOS[#]	56.00	56.00	112.00
None of the Above Indications	28.00	28.00	56.00

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

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Table 7a
Etoricoxib Prescribing over a 1-year Period of Follow-up
Number of Days of Therapy, by Inferred Indication

Inferred Indication	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Osteoarthritis (OA)			
N	13752	14678	3698
Mean	113.61	97.49	155.50
Std. Deviation	113.49	107.01	125.71
Minimum	1.00	1.00	1.00
25th Percentile	28.00	28.00	28.00
Median	56.00	42.00	112.00
75th Percentile	168.00	140.00	280.00
Maximum	365.00	365.00	365.00
Rheumatoid arthritis (RA)			
N	1181	1435	475
Mean	158.35	133.09	203.37
Std. Deviation	127.12	121.51	127.45
Minimum	5.00	5.00	7.00
25th Percentile	30.00	28.00	68.00
Median	112.00	84.00	213.00
75th Percentile	285.00	225.00	336.00
Maximum	365.00	365.00	365.00
Gout			
N	2877	6205	1047
Mean	52.67	37.08	65.42
Std. Deviation	70.68	52.58	83.98
Minimum	3.00	1.00	1.00
25th Percentile	14.00	14.00	14.00
Median	28.00	21.00	28.00
75th Percentile	56.00	37.33	74.00
Maximum	365.00	365.00	365.00
Ankylosing spondylitis (AS)			
N	286	597	154
Mean	170.69	154.78	197.71
Std. Deviation	125.77	118.12	125.95
Minimum	7.00	7.00	7.00
25th Percentile	56.00	56.00	56.00
Median	166.00	127.00	196.00
75th Percentile	288.00	267.00	331.00
Maximum	365.00	365.00	365.00
More than one OA RA Gout or AS diagnoses			
N	2278	2518	687
Mean	115.16	93.73	155.23
Std. Deviation	113.60	106.83	124.93
Minimum	4.00	3.00	7.00
25th Percentile	28.00	28.00	30.00
Median	56.00	28.00	112.00
75th Percentile	180.00	112.00	280.00
Maximum	365.00	365.00	365.00

Table 7a (cont.)
Etoricoxib Prescribing over a 1-year Period of Follow-up
Number of Days of Therapy, by Inferred Indication

Inferred Indication	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Arthritis NOS[#]			
N	1709	2395	513
Mean	110.09	101.52	162.07
Std. Deviation	114.19	107.81	128.32
Minimum	4.00	1.00	7.00
25th Percentile	28.00	28.00	56.00
Median	56.00	56.00	112.00
75th Percentile	168.00	140.00	300.00
Maximum	365.00	365.00	365.00
None of the Above Indications			
N	11172	18106	1885
Mean	70.41	63.96	129.08
Std. Deviation	87.49	79.82	120.57
Minimum	1.00	1.00	3.00
25th Percentile	28.00	28.00	28.00
Median	28.00	28.00	56.00
75th Percentile	65.67	56.00	214.00
Maximum	365.00	365.00	365.00

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

The distribution of the number of days of etoricoxib therapy over one year of follow-up, stratified by gender and stratified by age is shown in **Table 8**. Patients with missing values for duration of prescription were imputed to have the median value for their indication group, as previously described. The distributions are skewed, with mean values much higher than the median values for all sub-groups in all sub-cohorts.

In Sub-cohort 2, the median number of days of etoricoxib therapy over one year of follow-up were the same for men compared with women, and for those age <65 years compared with those ≥65 years old. In Sub-cohort 3, the median number of days of etoricoxib therapy over one year of follow-up was greater for women compared with men (112 vs.70, respectively), and it was the same in those age <65 years compared with those ≥65 years old (84 days).

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Table 8
Etoricoxib Prescribing over a 1-year Period of Follow-up
Number of Days of Therapy
Stratified by Gender and by Age Group

	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Men			
N	13136	19748	3437
Mean	89.30	70.80	131.24
Std. Deviation	103.29	90.43	122.83
Minimum	2.00	1.00	1.00
25th Percentile	28.00	28.00	28.00
Median	30.00	28.00	70.00
75th Percentile	112.00	70.00	224.00
Maximum	365.00	365.00	365.00
Women			
N	20119	26185	5022
Mean	100.10	83.39	149.86
Std. Deviation	108.19	98.24	125.94
Minimum	1.00	1.00	1.00
25th Percentile	28.00	28.00	28.00
Median	56.00	28.00	112.00
75th Percentile	140.00	84.00	280.00
Maximum	365.00	365.00	365.00
Age < 65 Years			
N	19337	30195	4870
Mean	92.16	78.44	145.75
Std. Deviation	104.36	94.73	125.58
Minimum	1.00	1.00	1.00
25th Percentile	28.00	28.00	28.00
Median	30.00	28.00	84.00
75th Percentile	112.00	84.00	267.00
Maximum	365.00	365.00	365.00
Age >=65 Years			
N	13918	15739	3589
Mean	100.93	77.08	137.61
Std. Deviation	109.00	95.98	124.10
Minimum	1.00	1.00	1.00
25th Percentile	28.00	28.00	28.00
Median	56.00	28.00	84.00
75th Percentile	140.00	84.00	238.00
Maximum	365.00	365.00	365.00

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

The distribution of the number of days of etoricoxib therapy over a one-year period of follow-up is shown by initial dose of etoricoxib in Table 9. For Sub-cohorts 1 and 2 the duration of etoricoxib prescribing pertains to the initial etoricoxib prescription before and after the Urgent Safety Restriction, respectively. For Sub-cohort 3, it pertains to the first etoricoxib prescription following the Urgent Safety Restriction (not the initial etoricoxib prescription, which would have occurred during the first sub-cohort calendar time period). This analysis includes only those patients who did not later switch to a different dose of etoricoxib. Patients with missing values for duration of prescription were imputed to have the median value for their indication group.

The distributions are skewed, with mean values much higher than the median values for all levels of initial etoricoxib dose in all sub-cohorts. Patients in Sub-cohort 2 who did not later switch to a different dose used etoricoxib 30, 60, 90, and 120 mg for a median of 28, 28, 28, and 14 days, respectively. Patients in Sub-cohort 3 who did not later switch to a different dose used etoricoxib 60, 90, and 120 mg for a median of 100, 112 and 28 days, respectively. The upper end of the therapy duration range was 365 days for all of the above subgroups.

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Table 9
Etoricoxib Prescribing over a 1-year Period of Follow-up
Number of Days of Therapy
By Initial Etoricoxib Dose[#]

	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Etoricoxib 30 mg			
N	0	3755	0
Mean	0.00	74.85	0.00
Std. Deviation	0.00	88.22	0.00
Minimum	0.00	2.00	0.00
25th Percentile	0.00	28.00	0.00
Median	0.00	28.00	0.00
75th Percentile	0.00	84.00	0.00
Maximum	0.00	365.00	0.00
Etoricoxib 60 mg			
N	16107	17360	2844
Mean	90.23	76.09	147.89
Std. Deviation	100.32	90.17	123.62
Minimum	1.00	1.00	1.00
25th Percentile	28.00	28.00	28.00
Median	30.00	28.00	100.00
75th Percentile	112.00	84.00	268.50
Maximum	365.00	365.00	365.00
Etoricoxib 90 mg			
N	7383	11121	1539
Mean	96.61	78.11	159.46
Std. Deviation	106.01	92.75	125.17
Minimum	1.00	1.00	7.00
25th Percentile	28.00	28.00	40.00
Median	35.00	28.00	112.00
75th Percentile	140.00	84.00	280.00
Maximum	365.00	365.00	365.00
Etoricoxib 120 mg			
N	4187	7381	599
Mean	38.76	26.89	61.99
Std. Deviation	60.99	41.24	84.99
Minimum	1.00	1.00	1.00
25th Percentile	7.00	7.00	14.00
Median	21.00	14.00	28.00
75th Percentile	28.00	28.00	63.00
Maximum	365.00	365.00	365.00

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

Medication Possession Ratio

Table 10 shows the median medication possession ratio (MPR; defined as the proportion of days over one year covered by etoricoxib prescriptions) of etoricoxib by indication. For Sub-cohorts 1 and 2 the MPR pertains to the initial etoricoxib prescription before and after the Urgent Safety Restriction, respectively. For Sub-cohort 3, it pertains to the first etoricoxib prescription following the Urgent Safety Restriction (not the initial etoricoxib prescription, which would have occurred during the first sub-cohort calendar time period). This analysis includes **only** those patients who did not later switch to a different dose of etoricoxib. Median values are shown because the distribution is highly skewed, with mean values much higher than the median values for all indications in all sub-cohorts. All univariate statistics regarding this parameter are shown by indication in **Table 10a**. Patients with missing values for duration of prescription were imputed to have the median value for their indication group.

For patients in Sub-cohort 2, the MPRs are higher in patients with RA and AS compared with other indications or patients with no recorded indications. The lowest ratios are seen in patients with Gout and with no recorded indications.

For patients in Sub-cohort 3, the MPRs are higher in patients with RA and AS compared with other indications or patients with no recorded indications. The lowest ratio is seen in patients with Gout. Compared with Sub-cohort 2, patients in Sub-cohort 3 have higher medication possession ratios for all indication groups.

The MPRs for etoricoxib (all indications combined) by sub-cohort were repeated with exclusion of:
- Patients with imputed values for duration of therapy (**Table 10b** in **Annex 3, Part A).** These results are similar to those shown in **Table 10**.
- Patients who switched to other NSAIDs (**Table 10c** in **Annex 3, Part A)**.

Lastly, the MPRs for etoricoxib (all indications combined) were examined using all available follow-up time **(Table 10d in Annex 3, Part A).**

Table 10
Etoricoxib Prescribing over a 1-year Period of Follow-up
Median Medication Possession Ratio[††] by Inferred Indication

Inferred Indication	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Osteoarthritis (OA)	0.15	0.15	0.31
Rheumatoid arthritis (RA)	0.31	0.23	0.61
Gout	0.08	0.06	0.08
Ankylosing spondylitis (AS)	0.46	0.38	0.55
More than one OA RA Gout or AS diagnoses	0.15	0.12	0.31
Arthritis NOS[#]	0.15	0.15	0.31
None of the Above Indications	0.08	0.08	0.23

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

[††] Medication Possession Ratio = Proportion of days over one year covered by etoricoxib prescriptions.

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Table 10a
Etoricoxib Prescribing over a 1-year Period of Follow-up
Medication Possession Ratio[††] by Inferred Indication

Inferred Indication	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Osteoarthritis (OA)			
N	13752	14678	3698
Mean	0.32	0.28	0.44
Std. Deviation	0.32	0.30	0.35
Minimum	0.00	0.00	0.00
25th Percentile	0.08	0.08	0.11
Median	0.15	0.15	0.31
75th Percentile	0.54	0.38	0.79
Maximum	1.00	1.00	1.00
Rheumatoid arthritis (RA)			
N	1181	1435	475
Mean	0.45	0.38	0.57
Std. Deviation	0.35	0.34	0.35
Minimum	0.02	0.01	0.02
25th Percentile	0.12	0.08	0.23
Median	0.31	0.23	0.61
75th Percentile	0.82	0.69	0.92
Maximum	1.00	1.00	1.00
Gout			
N	2877	6205	1047
Mean	0.15	0.11	0.19
Std. Deviation	0.20	0.16	0.24
Minimum	0.01	0.01	0.02
25th Percentile	0.04	0.04	0.04
Median	0.08	0.06	0.08
75th Percentile	0.15	0.12	0.22
Maximum	1.00	1.00	1.00
Ankylosing spondylitis (AS)			
N	286	597	154
Mean	0.49	0.45	0.55
Std. Deviation	0.35	0.33	0.35
Minimum	0.02	0.02	0.02
25th Percentile	0.15	0.15	0.15
Median	0.46	0.38	0.55
75th Percentile	0.83	0.77	0.91
Maximum	1.00	1.00	1.00
More than one OA RA Gout or AS diagnoses			
N	2278	2518	687
Mean	0.32	0.27	0.43
Std. Deviation	0.32	0.30	0.35
Minimum	0.01	0.01	0.02
25th Percentile	0.08	0.08	0.09
Median	0.15	0.12	0.31
75th Percentile	0.54	0.38	0.78
Maximum	1.00	1.00	1.00

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Table 10a
Etoricoxib Prescribing over a 1-year Period of Follow-up
Medication Possession Ratio[††] by Inferred Indication

Inferred Indication	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)	Sub-cohort 3[§] (N=8459)
Arthritis NOS[#]			
N	1709	2395	513
Mean	0.32	0.29	0.45
Std. Deviation	0.32	0.31	0.35
Minimum	0.02	0.01	0.02
25th Percentile	0.08	0.08	0.15
Median	0.15	0.15	0.31
75th Percentile	0.49	0.46	0.84
Maximum	1.00	1.00	1.00
None of the Above Indications			
N	11172	18106	1885
Mean	0.21	0.20	0.37
Std. Deviation	0.26	0.24	0.34
Minimum	0.00	0.01	0.01
25th Percentile	0.08	0.08	0.08
Median	0.08	0.08	0.23
75th Percentile	0.23	0.19	0.62
Maximum	1.00	1.00	1.00

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

[††] Medication Possession Ratio = Proportion of days over one year covered by etoricoxib prescriptions.

The distribution of MPR of etoricoxib by initial dose is shown in **Table 11**. The distribution is highly skewed for all indications, with mean values much higher than the median values for all levels of initial etoricoxib dose in all sub-cohorts. This analysis includes **only** those patients who did not later switch to a different dose of etoricoxib. Patients with missing values for duration of prescription were imputed to have the median value for their indication group. Etoricoxib 30 mg was not available for patients in Sub-cohort 1 and hence not available for patients in Sub-cohort 3.

For patients in Sub-cohort 2, the MPRs are similar for initial doses of 30, 60 and 90 mg, while the MPR is lower for 120 mg. A similar pattern is seen for patients in Sub-cohort 3.

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Table 11
Etoricoxib Prescribing over a 1-year Period of Follow-up
Medication Possession Ratio††
By Initial Etoricoxib Dose#

	Sub-cohort 1† (N=33255)	Sub-cohort 2‡ (N=45934)	Sub-cohort 3§ (N=8459)
Etoricoxib 30 mg			
N	0	3755	0
Mean	0.00	0.23	0.00
Std. Deviation	0.00	0.26	0.00
Minimum	0.00	0.01	0.00
25th Percentile	0.00	0.08	0.00
Median	0.00	0.08	0.00
75th Percentile	0.00	0.23	0.00
Maximum	0.00	1.00	0.00
Etoricoxib 60 mg			
N	16107	17360	2844
Mean	0.26	0.23	0.42
Std. Deviation	0.29	0.26	0.34
Minimum	0.00	0.01	0.00
25th Percentile	0.08	0.08	0.12
Median	0.12	0.08	0.31
75th Percentile	0.33	0.23	0.77
Maximum	1.00	1.00	1.00
Etoricoxib 90 mg			
N	7383	11121	1539
Mean	0.28	0.23	0.45
Std. Deviation	0.30	0.27	0.34
Minimum	0.00	0.01	0.02
25th Percentile	0.08	0.08	0.15
Median	0.15	0.08	0.38
75th Percentile	0.38	0.27	0.79
Maximum	1.00	1.00	1.00
Etoricoxib 120 mg			
N	4187	7381	599
Mean	0.12	0.08	0.18
Std. Deviation	0.18	0.13	0.24
Minimum	0.00	0.00	0.02
25th Percentile	0.02	0.02	0.04
Median	0.06	0.04	0.08
75th Percentile	0.10	0.08	0.21
Maximum	1.00	1.00	1.00

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

§ First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

†† Medication Possession Ratio = Proportion of days over one year covered by etoricoxib prescriptions.

Patients prescribed a different dose of etoricoxib following their initial excluded.

The MPRs for etoricoxib in each sub-cohort (all indications combined), by gender, and by age are shown in **Table 12**.

Patients in Sub-cohort 2 have similar MPRs regardless of gender or age. In Sub-cohort 3, women have somewhat higher MPRs than men, and younger patients have slightly higher MPRs than older patients.

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Table 12
Etoricoxib Prescribing over a 1-year Period of Follow-up
Medication Possession Ratio††
Stratified by Gender and by Age Group

	Sub-cohort 1† (N=33255)	Sub-cohort 2‡ (N=45934)	Sub-cohort 3§ (N=8459)
Men			
N	13136	19748	3437
Mean	0.26	0.21	0.37
Std. Deviation	0.29	0.26	0.34
Minimum	0.01	0.00	0.01
25th Percentile	0.08	0.08	0.08
Median	0.10	0.08	0.23
75th Percentile	0.33	0.23	0.65
Maximum	1.00	1.00	1.00
Women			
N	20119	26185	5022
Mean	0.29	0.24	0.42
Std. Deviation	0.30	0.28	0.35
Minimum	0.00	0.01	0.00
25th Percentile	0.08	0.08	0.08
Median	0.15	0.08	0.31
75th Percentile	0.42	0.31	0.77
Maximum	1.00	1.00	1.00
Age < 65 Years			
N	19337	30195	4870
Mean	0.26	0.23	0.41
Std. Deviation	0.29	0.27	0.35
Minimum	0.00	0.00	0.01
25th Percentile	0.08	0.08	0.08
Median	0.10	0.08	0.27
75th Percentile	0.35	0.24	0.77
Maximum	1.00	1.00	1.00
Age >=65 Years			
N	13918	15739	3589
Mean	0.29	0.23	0.39
Std. Deviation	0.31	0.28	0.34
Minimum	0.00	0.01	0.00
25th Percentile	0.08	0.08	0.08
Median	0.15	0.08	0.23
75th Percentile	0.46	0.26	0.70
Maximum	1.00	1.00	1.00

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

§ First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

†† Medication Possession Ratio = Proportion of days over one year covered by etoricoxib prescriptions

Dose Changes and Switching

Table 13 shows etoricoxib dose changes and switches to other NSAIDs or Coxibs over a one-year period following the initial etoricoxib prescription. For Sub-cohorts 1 and 2 this analysis pertains to the initial etoricoxib prescription before and after the Urgent Safety Restriction, respectively. For Sub-cohort 3, it pertains to the first etoricoxib prescription following the Urgent Safety Restriction (not the initial etoricoxib prescription, which would have occurred during the first sub-cohort calendar time period).

In Sub-cohort 2, 4.6%, 4.0%, and 31.7% of patients had an etoricoxib dose increase, decrease, or switch to another non-steroidal anti-inflammatory treatment, respectively. In Sub-cohort 3, 17.8%, 16.5%, and 31.7% of patients had an etoricoxib dose increase, decrease, or switch to another non-steroidal anti-inflammatory treatment, respectively.

Table 13
Changes in Etoricoxib Dose or Type of NSAID / Coxib
Over a 1 Year Period of Follow-up

	Sub-cohort 1[†] (N = 33255) n (%)	Sub-cohort 2[‡] (N = 45934) n (%)	Sub-cohort 3[§] (N = 8459) n (%)
Dose Increased	1928 (5.80)	2133 (4.64)	1510 (17.85)
Dose Decreased	1240 (3.73)	1819 (3.96)	1393 (16.47)
Switch to other NSAIDS	12363 (37.18)	14565 (31.71)	2683 (31.72)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[§] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005 and at least one additional etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

When the above analysis was repeated to include all follow-up time after the initial etoricoxib prescription, somewhat larger percentages of patients had etoricoxib dose increases or decreases in Sub-cohorts 2 and 3, while a much larger percentage of patients switched to another NSAID or Coxib in these two sub-cohorts. Sub-cohort 3 had the highest proportion of patients with etoricoxib dose changes or switches to another NSAID or Coxib in this analysis. (**Table 13a** in **Annex 3, Part A**)

10.4. Main results

Clinical Outcomes

Examination of the incidence rates of primary clinical outcomes (new events in previously undiagnosed patients) after the initial course of etoricoxib therapy and during the first year of follow-up affords the most unbiased examination of rates after the Urgent Safety Restriction. Sub-cohort 3 was not included in this analysis because by definition these patients' initial course of etoricoxib therapy was included in the analyses of Sub-cohort 1 (with the exception of those patients who continuously used etoricoxib before and after the Urgent Safety Restriction, in which case their initial course would extend post-Urgent Safety Restriction and would not be included in the analyses of Sub-cohort 1).

The incidence **per 1000 person-years** (py) and associated 95% confidence intervals (95% CI) of primary clinical outcomes is shown in **Table 14**. Note that the number of patients at risk varies by type of event within a sub-cohort based on exclusion of patients with a prior history of disease (at any time) from these analyses. Note also that the incidence rates for many events are based on small numbers; as a result there is inherent variability as evidenced by wide CIs for some of the specific clinical outcome event rates, across the different calendar-time periods of study.

In the following narrative the incidence of clinical outcomes in Sub-cohort 2 is specifically described, since these results pertain to the patients who have most recently been initiated on etoricoxib therapy, following the Urgent Safety Restriction of 2005. The frequency of events is described here according to the following guidelines (per Council for International Organizations of Medical Sciences, CIOMS -- http://www.cioms.ch/publications/reporting_adverse_drug.pdf):

- very common >10%/yr
- common >1% and <10%/yr
- uncommon >0.1% and <1.0%/yr
- rare >0.01% and < 0.1%/yr
- very rare <0.01%/yr.

Gastrointestinal clinical events (perforation, ulcers, or bleeding) were uncommon in Sub-cohort 2 (patients initially prescribed etoricoxib after the Urgent Safety Restriction) (6.5/1000py), whereas prescriptions for new gastrointestinal medications were common (52.6/1000py). This high prevalence of gastroprotective medication use among new etoricoxib users since the Urgent Safety Restriction may be a reflection of channelling of patients with high risk of GI events to etoricoxib therapy or changes in practice patterns over time with respect to GI protection in patients being treated with COX-2 inhibitors, or both.

In Sub-cohort 2 (patients initially prescribed etoricoxib after the Urgent Safety Restriction) new diagnoses of edema were common in Sub-cohort 2 (21.2.0/1000py), while acute renal impairment or failure (about 2.4/1000py) and congestive heart failure (2.8/1000py) were uncommon. Overall, cardiovascular system events were common 11.6/1000py); whereas specific cardiovascular diagnoses each occurred rarely to uncommonly. Coronary heart disease events (mostly MI) occurred at a rate of 2.7/1000py. Overall, cerebrovascular events occurred at a rate of (5.8/1000py); the most

frequent specific cerebrovascular events were strokes not specified as ischemic or haemorrhagic and TIAs, which occurred at rates of about 2.2-3.5/1000py. DVT and PE were uncommon, with rates of 3.7 and 1.3/1000py, respectively. Sudden deaths were rare. The combination of any acute vascular event or sudden death, provided for completeness, was common and occurred at a rate of about (11.9/1000py).

Also in Sub-cohort 2 (patients initially prescribed etoricoxib after the Urgent Safety Restriction), new hypertension, as measured by only a new diagnosis in the patient record, was common (29.9/1000py). On the other hand, the incidence rate of new hypertension, as measured by both a new diagnoses and concomitant prescription of antihypertensive therapy in the patient record was 17.1/1000py; this dual definition of incident hypertension may reflect a more accurate rate of clinically important hypertension than that based on a diagnosis alone. The incidence of blood pressure (BP) measurement was very common and occurred at a rate of 104.0/1000py. Note that this analysis excluded persons with prior events, so in the case of BP measurement the above rate does not include those patients who had their BP measured during the baseline period (within 12 months prior to their first etoricoxib prescription); see below for analyses of the incidence of BP measurement that includes persons with a baseline history of BP measurement.

It should be noted that in comparison to Sub-cohort 1 which had their initial prescriptions for etoricoxib before the Urgent Safety Restriction, Sub-cohort 2 had lower rates of new diagnoses for several of the clinical outcomes as well as higher rates of GI and CV medication use and blood pressure measurements.

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Table 14
Incidence Rate of Clinical Outcomes
First Year Follow-up and First Course Exposure
Patients without Prior Events

Outcome	Sub-cohort 1[†]		Sub-cohort 2[‡]	
	n/N	Incidence Rate[††] (95% CI)	n/N	Incidence Rate[††] (95% CI)
Gastrointestinal (GI)				
Gastrointestinal Disease	81/31139	10.93 (8.68, 13.59)	56/43325	6.53 (4.93, 8.48)
Gastrointestinal Medication	102/15354	30.04 (24.49, 36.47)	161/17041	52.59 (44.78, 61.37)
Renovascular				
Edema	133/28736	19.80 (16.57, 23.46)	167/40141	21.23 (18.13, 24.71)
Renal Impairment/Failure	19/33111	2.41 (1.45, 3.76)	22/45661	2.43 (1.52, 3.67)
Congestive Heart Failure				
Heart failure/Left ventricular dysfunction	37/32384	4.78 (3.37, 6.59)	25/45201	2.78 (1.80, 4.10)
Acute Vascular Events				
Cardiovascular System Event	99/29653	14.05 (11.42, 17.11)	97/41843	11.63 (9.43, 14.19)
Coronary Heart Disease	33/31788	4.35 (2.99, 6.11)	24/44408	2.71 (1.74, 4.03)
Acute Myocardial Infarction	30/32070	3.92 (2.64, 5.59)	23/44664	2.58 (1.64, 3.88)
Unstable angina pectoris	7/32805	0.90 (0.36, 1.84)	2/45509	0.22 (0.03, 0.80)
Cerebrovascular Event	49/31924	6.44 (4.77, 8.52)	51/44494	5.77 (4.30, 7.59)
Intracerebral Haemorrhage	4/33209	0.50 (0.14, 1.29)	2/45875	0.22 (0.03, 0.79)
Cerebral Infarction	7/33095	0.89 (0.36, 1.83)	11/45703	1.21 (0.61, 2.17)
Cerebrovascular Accident NOS[‡‡]	22/32778	2.81 (1.76, 4.26)	20/45413	2.22 (1.36, 3.43)
Transient Ischemic Attack	34/32388	4.41 (3.05, 6.16)	31/45017	3.47 (2.36, 4.92)
Arterial embolism / thrombosis	1/33215	0.13 (0.00, 0.70)	0/45904	0.00 (n/a, n/a)
Deep Venous Thrombosis	28/32343	3.64 (2.42, 5.25)	33/44824	3.72 (2.56, 5.22)
Pulmonary Embolism	12/32946	1.53 (0.79, 2.67)	12/45477	1.33 (0.69, 2.32)
Sudden/unexplained death				
Sudden/unexplained death	2/33186	0.25 (0.03, 0.91)	3/45878	0.33 (0.07, 0.96)
Acute Vascular event or sudden death				
Any acute vascular event or sudden/unexplained death	100/29596	14.23 (11.58, 17.30)	99/41795	11.89 (9.66, 14.47)
Hypertension				
Diagnosis only	233/23638	43.22 (37.85, 49.14)	190/32625	29.86 (25.77, 34.42)
Diagnosis + medication	163/28534	24.40 (20.80, 28.45)	131/38982	17.11 (14.30, 20.30)
Cardiovascular medication				
Cardiovascular medication	35/14492	10.90 (7.59, 15.15)	56/20159	14.54 (10.98, 18.88)
Blood Pressure				
Blood Pressure Measurement	18/1478	58.69 (34.78, 92.76)	19/1094	104.00 (62.61, 162.40)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

[††] Per 1000 person year

The same analyses as above were repeated with stratification by age <65 vs. ≥65 years (Table 14a and Table 14b in Annex 3, Part A). As expected, in Sub-cohort 2 (patients initially prescribed etoricoxib after the Urgent Safety Restriction), the occurrence of clinical outcomes was greater in the older age stratum compared with the younger.

The incidence rates of clinical outcomes by initial dose of etoricoxib (30, 60, 90, 120 mg) are shown in **Tables 14c through 14f** in the **Annex 3, Part A.** In general, the interpretation of the results is limited by sparse data, especially at the 30 and 120 mg dose level. Comparisons of rates across doses is difficult due to the wide 95% CIs observed for most dose-specific rates of clinical outcomes. In addition, since dose of etoricoxib is related to indication, which in turn may be related to risk factors for many of the clinical outcomes, comparisons of rates across doses is confounded by differences in the background risk of events.

A sensitivity analysis of the incidence rates of new onset clinical outcomes (excluding patients with prior events) during the first course of etoricoxib therapy and first year of follow-up was conducted by censoring patient follow-up for events on the date that a new prescription for a NSAID other than etoricoxib was written. (**Table 15**) Results of these same sensitivity analyses stratified by age and stratified by initial dose are shown in **Tables 15a through 15f** (in **Annex 3, Part A**).

Table 15
Incidence Rate of Clinical Outcomes
First Year Follow-up and First Course Exposure
Exposure Truncated when Other NSAIDs Prescription Written
Patients without Prior Events

Outcome	Sub-cohort 1[†]		Sub-cohort 2[‡]	
	n/N	Incidence Rate[††] (95% CI)	n/N	Incidence Rate[††] (95% CI)
Gastrointestinal (GI)				
Gastrointestinal Disease	74/31139	10.81 (8.48, 13.57)	54/43325	6.72 (5.05, 8.77)
Gastrointestinal Medication	92/15354	28.85 (23.26, 35.39)	150/17041	51.79 (43.84, 60.78)
Renovascular				
Edema	125/28736	20.05 (16.69, 23.88)	154/40141	20.85 (17.69, 24.42)
Renal Impairment/Failure	17/33111	2.33 (1.35, 3.72)	20/45661	2.35 (1.44, 3.63)
Congestive Heart Failure				
Heart failure/Left ventricular dysfunction	35/32384	4.88 (3.40, 6.79)	24/45201	2.85 (1.82, 4.24)
Acute Vascular Events				
Cardiovascular System Event	91/29653	13.95 (11.23, 17.13)	93/41843	11.89 (9.59, 14.56)
Coronary Heart Disease	30/31788	4.27 (2.88, 6.10)	23/44408	2.77 (1.76, 4.15)
Acute Myocardial Infarction	27/32070	3.81 (2.51, 5.54)	22/44664	2.64 (1.65, 3.99)
Unstable angina pectoris	6/32805	0.83 (0.30, 1.80)	2/45509	0.24 (0.03, 0.85)
Cerebrovascular Event	45/31924	6.39 (4.66, 8.56)	47/44494	5.67 (4.17, 7.54)
Intracerebral Haemorrhage	4/33209	0.55 (0.15, 1.40)	2/45875	0.23 (0.03, 0.85)
Cerebral Infarction	5/33095	0.68 (0.22, 1.60)	9/45703	1.06 (0.48, 2.01)
Cerebrovascular Accident NOS[‡‡]	21/32778	2.90 (1.80, 4.44)	17/45413	2.01 (1.17, 3.22)
Transient Ischemic Attack	32/32388	4.48 (3.07, 6.33)	30/45017	3.58 (2.41, 5.11)
Arterial embolism / thrombosis	1/33215	0.14 (0.00, 0.76)	0/45904	0.00 (n/a, n/a)
Deep Venous Thrombosis	26/32343	3.65 (2.38, 5.35)	33/44824	3.96 (2.73, 5.57)
Pulmonary Embolism	11/32946	1.51 (0.76, 2.71)	12/45477	1.42 (0.73, 2.48)
Sudden/unexplained death				
Sudden/unexplained death	2/33186	0.27 (0.03, 0.99)	3/45878	0.35 (0.07, 1.03)
Acute Vascular event or sudden death				
Any acute vascular event or sudden/unexplained death	92/29596	14.14 (11.40, 17.34)	95/41795	12.16 (9.84, 14.86)
Hypertension				
Diagnosis only	217/23638	43.35 (37.77, 49.51)	179/32625	29.85 (25.64, 34.55)
Diagnosis + medication	156/28534	25.19 (21.39, 29.47)	124/38982	17.23 (14.33, 20.55)
Cardiovascular medication				
Cardiovascular medication	33/14492	11.01 (7.58, 15.46)	53/20159	14.50 (10.86, 18.97)
Blood Pressure				
Blood Pressure Measurement	17/1478	58.74 (34.22, 94.05)	18/1094	101.81 (60.34, 160.91)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005
[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013
[#] NOS=Not otherwise specified
[††] Per 1000 person year

Table 16 shows results of analyses of clinical outcomes during the first course of etoricoxib therapy and first year of follow-up, including patients with prior events of interest, but with censoring of patient follow-up for events on the date that a new prescription for a NSAID other than etoricoxib is written.

As expected, the rates of many types of clinical events are higher in this analysis compared with the analysis that excluded patients with a history of events prior to initiating etoricoxib treatment (see **Table 15**). In particular, among patients in Sub-cohort 2 (patients initially prescribed etoricoxib after the Urgent Safety Restriction) the incidences of GI medications and cardiovascular medication are substantially higher in this analysis compared with that shown in **Table 15**. The incidence of blood pressure (BP) measurement was very common and occurred at a rate of 92.9/1000py.

Table 17 (in **Annex 3, Part A**) shows the results of the analyses of the incidence of clinical outcomes when all courses of exposure were considered over one year. Comparisons of incidence rates from this analysis to those of the first course of therapy only (shown in **Table 15**) may be biased because the risk of some events may be affected by changing medical history over time and by prior treatment with etoricoxib, resulting in the potential for the hazard function for a specific event to change over time. The same potential bias exists when comparing among sub-cohorts in this analysis.

Table 18 (in **Annex 3, Part A**) shows the results of the analyses of the incidence of clinical outcomes when all available follow-up and all courses of exposure were considered. Comparisons of incidence rates from this analysis to those of the first course of therapy only, and comparisons of incidence rates among sub-cohorts in this analysis, may also be biased for the reasons stated above.

Table 16
Incidence Rate of Clinical Outcomes
First Year Follow-up and First Course Exposure
Exposure Truncated when Other NSAIDs Prescription Written
Includes Patients with Prior Event

Outcome	Sub-cohort 1[†]		Sub-cohort 2[‡]	
	n/N	Incidence Rate[††] (95% CI)	n/N	Incidence Rate[††] (95% CI)
Gastrointestinal (GI)				
Gastrointestinal Disease	85/33255	11.59 (9.26, 14.33)	61/45934	7.15 (5.47, 9.18)
Gastrointestinal Medication	326/33255	44.61 (39.90, 49.72)	846/45934	100.16 (93.52, 107.14)
Renovascular				
Edema	205/33255	28.11 (24.39, 32.23)	269/45934	31.68 (28.00, 35.70)
Renal Impairment/Failure	19/33255	2.59 (1.56, 4.04)	23/45934	2.69 (1.71, 4.04)
Congestive Heart Failure				
Heart failure/Left ventricular dysfunction	60/33255	8.18 (6.24, 10.53)	31/45934	3.63 (2.47, 5.15)
Acute Vascular Events				
Cardiovascular System Event	142/33255	19.40 (16.34, 22.87)	126/45934	14.79 (12.32, 17.60)
Coronary Heart Disease	45/33255	6.13 (4.47, 8.21)	29/45934	3.40 (2.27, 4.88)
Acute Myocardial Infarction	41/33255	5.59 (4.01, 7.58)	28/45934	3.28 (2.18, 4.74)
Unstable angina pectoris	8/33255	1.09 (0.47, 2.15)	3/45934	0.35 (0.07, 1.03)
Cerebrovascular Event	66/33255	9.00 (6.96, 11.46)	56/45934	6.56 (4.96, 8.52)
Intracerebral Haemorrhage	4/33255	0.54 (0.15, 1.40)	2/45934	0.23 (0.03, 0.85)
Cerebral Infarction	5/33255	0.68 (0.22, 1.59)	10/45934	1.17 (0.56, 2.15)
Cerebrovascular Accident NOS[‡‡]	28/33255	3.82 (2.54, 5.51)	19/45934	2.22 (1.34, 3.47)
Transient Ischemic Attack	40/33255	5.46 (3.90, 7.43)	34/45934	3.98 (2.76, 5.57)
Arterial embolism / thrombosis	1/33255	0.14 (0.00, 0.76)	0/45934	0.00 (n/a, n/a)
Deep Venous Thrombosis	32/33255	4.36 (2.98, 6.16)	38/45934	4.45 (3.15, 6.11)
Pulmonary Embolism	12/33255	1.63 (0.84, 2.86)	12/45934	1.41 (0.73, 2.45)
Sudden/unexplained death				
Sudden/unexplained death	2/33255	0.27 (0.03, 0.98)	3/45934	0.35 (0.07, 1.03)
Acute Vascular event or sudden death				
Any acute vascular event or sudden/unexplained death	142/33255	19.40 (16.34, 22.87)	129/45934	15.14 (12.64, 17.99)
Hypertension				
Diagnosis only	376/33255	51.89 (46.78, 57.41)	247/45934	29.12 (25.60, 32.99)
Diagnosis + medication	214/33255	29.36 (25.56, 33.57)	153/45934	17.99 (15.25, 21.08)
Cardiovascular medication				
Cardiovascular medication	294/33255	40.21 (35.74, 45.08)	480/45934	56.50 (51.56, 61.78)
Blood Pressure				
Blood Pressure Measurement	354/33255	48.62 (43.69, 53.96)	781/45934	92.85 (86.45, 99.59)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005
[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013
[#] NOS=Not otherwise specified
[††] Per 1000 person year

10.5. Other analyses

At the request of MHRA, the MAH conducted some additional analyses for the 2015 report to 1) describe characteristics and health outcomes of interest in OA & RA patients taking standard doses and those taking higher than labelled doses in Sub-cohorts 1 and 2, and 2) describe characteristics and health outcomes of interest over time in Sub-cohort 2. Please note that only some of the tables are provided for the analyses of standard and higher than labelled doses, so the tables are numbered to match the tables in the primary analyses.

10.5.1 Description of characteristics and outcomes for OA & RA patients taking higher than indicated doses (HD) vs. standard doses (SD) of etoricoxib

For the purposes of these analyses, standard doses (SD) were considered to be 30 and 60 mg for OA and 30, 60, and 90 mg for RA. 90 and 120 mg were considered higher than indicated doses (HD) for OA; 120 mg was considered high dose for RA. The discussion primarily focuses on Sub-cohort 2 since this cohort reflects the period where the 30 mg dose was available and represents the majority of the time period since market authorization.

Demographic characteristics for OA and RA patients taking HD and SD of etoricoxib are presented in **Tables 1HD and 1SD**. While fewer men than women took etoricoxib overall, men represented a higher percentage of those taking HD than SD in Sub-cohort 2: (34.7% of those taking HD and 27.7% of those taking SD were male). Those who took HD tended to be slightly younger on average than those who took SD in both sub-cohorts, with the percentages over age 65 lower for the HD group (43.5% of HD vs. 49.8% of SD for Sub-cohort 2). OA patients represented a higher percentage of those who took HD than those who took SD (97.6% of those taking HD and 87.9% of those who took SD had OA in Sub-cohort 2).

Tables 2HD and 2SD describe cardiovascular risk factors for OA and RA patients who took HD and SD of etoricoxib. In general, the characteristics (smoking status, BMI, blood pressure) of the two dose groups were very similar.

The baseline medical history of the HD and SD groups (**Tables 3HD and 3SD)** were generally similar, with both groups having similar rates of most conditions (e.g., CHF, cardiac events, cerebrovascular events, peripheral arterial disease, DVT, PE), and the HD group having a slightly lower rate of some conditions (e.g., GI events, edema, hypertension), and a slightly higher rate for history of diabetes for both sub-cohorts and dyslipidemia for Sub-cohort 1 compared to the SD group**.**

There were some differences in baseline medication use between the HD and SD groups as shown in **Tables 4HD and 4SD.** Use of non-selective NSAIDs was slightly higher and use of DMARDS and oral corticosteroids were slightly lower for the HD group than the SD group. At baseline, some of

the GI medications were used less in the HD sub-cohorts than in the SD groups. CV medication use was similar between the high and standard dose groups.

Tables 4 – 6 are not provided for this analysis.

Table 7HD/SD illustrates that the number of therapy days was lower for RA patients in the HD group than the SD group for Sub-cohort 1 and for both RA and OA patients in the HD group for Sub-cohort 2.

Tables 8-13 are not provided for this analysis.

Tables 14HD and 14SD provide incidence rates for the clinical outcomes in the first year of follow-up and first course of exposure to etoricoxib for the OA and RA patients with HD and SD respectively. Comparison of the incidence rates of the clinical outcomes between the HD and SD groups is challenging because there was considerable variation in the incidence rates of the clinical outcomes between Sub-cohorts 1 and 2 within both the HD and SD groups (e.g., for acute MI, the incidence rates for Sub-cohorts 1 and 2 for the HD group were quite different: 6.95 and 1.75 respectively, while the incidence rates for Sub-cohorts 1 and 2 for the SD group were much more similar: 3.55 and 2.96 respectively). The incidence rate for the HD group was somewhat higher than the SD group for some events and somewhat lower for others, but the pattern was often not the same for both sub-cohorts. In addition, many of the incidence rates were based on very small numbers of events with very large confidence intervals, and in most cases, the confidence intervals overlapped. Overall, there was no consistent pattern of a higher incidence of the clinical outcomes across both sub-cohorts for the HD group compared to the SD group.

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Table 1HD
Baseline Demographics and Indication for Etoricoxib, by Calendar Time Sub-cohort
Higher than indicated doses in OA and RA

Characteristic	Sub-cohort 1[†] (N=5027)	Sub-cohort 2[‡] (N=5312)
Indication for etoricoxib use n (%)		
Osteoarthritis	4930 (98.07)	5183 (97.57)
Rheumatoid arthritis	97 (1.93)	129 (2.43)
Gender n (%)		
Male	1745 (34.71)	1902 (35.81)
Female	3282 (65.29)	3410 (64.19)
Age (years)		
N	5027	5312
Mean	64.28	63.29
Std. Deviation	12.23	12.60
Minimum	16.73	20.70
25th Percentile	56.14	54.55
Median	64.32	63.02
75th Percentile	73.42	72.62
Maximum	98.57	101.04
Age<65 Years n (%)	2615 (52.02)	3000 (56.48)
Age>=65 Years n (%)	2412 (47.98)	2312 (43.52)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified as OA, RA, AS, or Gout

For OA, 90 and 120 mg will be considered higher than indicated; for RA, 120 mg will be considered higher than indicated

Table 1SD
Baseline Demographics and Indication for Etoricoxib, by Calendar Time Sub-cohort
Standard doses in OA and RA

Characteristic	Sub-cohort 1[†] (N=9906)	Sub-cohort 2[‡] (N=10801)
Indication for etoricoxib use n (%)		
Osteoarthritis	8822 (89.06)	9495 (87.91)
Rheumatoid arthritis	1084 (10.94)	1306 (12.09)
Gender n (%)		
Male	2740 (27.66)	3002 (27.79)
Female	7166 (72.34)	7799 (72.21)
Age (years)		
N	9906	10801
Mean	66.22	64.81
Std. Deviation	13.03	13.24
Minimum	14.55	15.93
25th Percentile	57.31	56.04
Median	66.86	64.92
75th Percentile	76.00	74.58
Maximum	101.27	103.63
Age<65 Years n (%)	4419 (44.61)	5424 (50.22)
Age>=65 Years n (%)	5487 (55.39)	5377 (49.78)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified as OA, RA, AS, or Gout

For OA, 90 and 120 mg will be considered higher than indicated; for RA, 120 mg will be considered higher than indicated

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Table 2HD
Baseline Cardiovascular Risk Factors by Calendar Time Sub-cohort
Higher than indicated doses in OA and RA

Characteristic	Sub-cohort 1[†] (N=5027)	Sub-cohort 2[‡] (N=5312)
Smoking Status n (%)		
Missing	318 (6.33)	41 (0.77)
Ex-Smoker	1204 (23.95)	1552 (29.22)
Non-Smoker	2461 (48.96)	2737 (51.52)
Smoker	1044 (20.77)	982 (18.49)
Body Mass Index(kg/m2)		
N	4345	4919
Mean	28.27	28.74
Std. Deviation	5.41	5.73
Minimum	15.20	15.00
25th Percentile	24.40	24.70
Median	27.50	27.80
75th Percentile	31.20	31.90
Maximum	53.90	53.90
< 20 n (%)	111 (2.21)	124 (2.33)
20-24 n (%)	1131 (22.50)	1205 (22.68)
25-29 n (%)	1746 (34.73)	1823 (34.32)
>= 30 n (%)	1357 (26.99)	1767 (33.26)
Missing n (%)	682 (13.57)	393 (7.40)
Systolic Blood Pressure (mmHg)		
N	4891	5250
Mean	138.18	134.03
Std. Deviation	18.23	15.82
Minimum	67.00	70.00
25th Percentile	127.00	123.00
Median	140.00	134.00
75th Percentile	150.00	143.00
Maximum	240.00	216.00
< 140 n (%)	2368 (47.11)	3181 (59.88)
140-149 n (%)	1284 (25.54)	1317 (24.79)
150-159 n (%)	596 (11.86)	425 (8.00)
>= 160 n (%)	643 (12.79)	327 (6.16)
Missing n (%)	136 (2.71)	62 (1.17)
Diastolic Blood Pressure (mmHg)		
N	4871	5246
Mean	80.28	78.61
Std. Deviation	9.57	9.19
Minimum	40.00	46.00
25th Percentile	75.00	72.00
Median	80.00	80.00
75th Percentile	86.00	84.00
Maximum	120.00	116.00
< 90 n (%)	3997 (79.51)	4616 (86.90)
>=90 n (%)	874 (17.39)	630 (11.86)
Missing n (%)	156 (3.10)	66 (1.24)

Characteristic	Sub-cohort 1† (N=5027)	Sub-cohort 2‡ (N=5312)
Number of Blood Pressure Measurements in prior 6 months		
N	2359	2646
Mean	2.01	1.89
Std. Deviation	1.64	1.55
Minimum	1.00	1.00
25th Percentile	1.00	1.00
Median	1.00	1.00
75th Percentile	2.00	2.00
Maximum	16.00	19.00
Missing n (%)	2668 (53.07)	2666 (50.19)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

For OA, 90 and 120 mg will be considered higher than indicated; for RA, 120 mg will be considered higher than indicated

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Table 2SD
Baseline Cardiovascular Risk Factors by Calendar Time Sub-cohort
Standard doses in OA and RA

Characteristic	Sub-cohort 1[†] (N=9906)	Sub-cohort 2[‡] (N=10801)
Smoking Status n (%)		
Missing	636 (6.42)	83 (0.77)
Ex-Smoker	2226 (22.47)	2952 (27.33)
Non-Smoker	5175 (52.24)	5837 (54.04)
Smoker	1869 (18.87)	1929 (17.86)
Body Mass Index(kg/m2)		
N	8433	9981
Mean	27.83	28.36
Std. Deviation	5.44	5.70
Minimum	15.20	15.00
25th Percentile	24.00	24.40
Median	27.00	27.50
75th Percentile	30.80	31.40
Maximum	53.90	53.70
< 20 n (%)	299 (3.02)	335 (3.10)
20-24 n (%)	2446 (24.69)	2601 (24.08)
25-29 n (%)	3232 (32.63)	3755 (34.77)
>= 30 n (%)	2456 (24.79)	3290 (30.46)
Missing n (%)	1473 (14.87)	820 (7.59)
Systolic Blood Pressure (mmHg)		
N	9628	10740
Mean	138.49	133.85
Std. Deviation	18.30	15.79
Minimum	63.00	75.00
25th Percentile	127.00	122.00
Median	140.00	134.00
75th Percentile	150.00	142.00
Maximum	233.00	220.00
< 140 n (%)	4580 (46.23)	6464 (59.85)
140-149 n (%)	2411 (24.34)	2731 (25.28)
150-159 n (%)	1322 (13.35)	896 (8.30)
>= 160 n (%)	1315 (13.27)	649 (6.01)
Missing n (%)	278 (2.81)	61 (0.56)
Diastolic Blood Pressure (mmHg)		
N	9607	10735
Mean	79.84	77.96
Std. Deviation	9.25	9.28
Minimum	40.00	40.00
25th Percentile	74.00	70.00
Median	80.00	80.00
75th Percentile	85.00	84.00
Maximum	138.00	131.00
< 90 n (%)	8004 (80.80)	9566 (88.57)
>=90 n (%)	1603 (16.18)	1169 (10.82)
Missing n (%)	299 (3.02)	66 (0.61)

Characteristic	Sub-cohort 1[†] (N=9906)	Sub-cohort 2[‡] (N=10801)
Number of Blood Pressure Measurements in prior 6 months		
N	4704	5505
Mean	2.02	1.87
Std. Deviation	1.72	1.60
Minimum	1.00	1.00
25th Percentile	1.00	1.00
Median	1.00	1.00
75th Percentile	2.00	2.00
Maximum	20.00	27.00
Missing n (%)	5202 (52.51)	5296 (49.03)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

For OA, 90 and 120 mg will be considered higher than indicated; for RA, 120 mg will be considered higher than indicated

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Table 3HD
Baseline Medical History by Calendar Time Sub-cohort
Higher than indicated doses in OA and RA

Medical History	Sub-cohort 1[†] (N=5027)	Sub-cohort 2[‡] (N=5312)
Gastrointestinal n (%)		
Gastrointestinal Ulcer, Perforation/Bleeding	367 (7.30)	357 (6.72)
Renovascular n (%)		
Kidney disease	52 (1.03)	479 (9.02)
Acute Renal Impairment/failure	12 (0.24)	28 (0.53)
Edema	846 (16.83)	783 (14.74)
Congestive Heart Failure n (%)		
Heart failure or Left Ventricular Dysfunction	125 (2.49)	86 (1.62)
Cardiac n (%)		
Myocardial Infarction	219 (4.36)	184 (3.46)
Unstable Angina Pectoris	491 (9.77)	351 (6.61)
Other (subacute) heart disease	592 (11.78)	440 (8.28)
Cerebrovascular n (%)		
Intracerebral / Subdural haemorrhage	6 (0.12)	5 (0.09)
Cerebral infarction	26 (0.52)	27 (0.51)
Cerebrovascular accident NOS[#]	83 (1.65)	66 (1.24)
Transient ischemic attack	152 (3.02)	151 (2.84)
Peripheral Arterial Disease n (%)		
Arterial embolism and thrombosis	13 (0.26)	5 (0.09)
Intermittent claudication	76 (1.51)	64 (1.20)
Peripheral vascular disease NOS[#]	86 (1.71)	54 (1.02)
Deep venous thrombosis n (%)		
Deep Venous Thrombosis	239 (4.75)	252 (4.74)
Pulmonary Embolism n (%)		
Pulmonary Embolism	61 (1.21)	62 (1.17)
Hypertension n (%)		
Hypertension	1714 (34.10)	1906 (35.88)
Dyslipidemia n (%)		
Dyslipidemia	660 (13.13)	852 (16.04)
Diabetes Mellitus n (%)		
Diabetes diagnostic code	414 (8.24)	523 (9.85)
Insulin prescription	95 (1.89)	104 (1.96)
Oral antidiabetic agent prescription	251 (4.99)	361 (6.80)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

For OA, 90 and 120 mg will be considered higher than indicated; for RA, 120 mg will be considered higher than indicated

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Table 3SD
Baseline Medical History by Calendar Time Sub-cohort
Standard doses in OA and RA

Medical History	Sub-cohort 1[†] (N=9906)	Sub-cohort 2[‡] (N=10801)
Gastrointestinal n (%)		
Gastrointestinal Ulcer, Perforation/Bleeding	760 (7.67)	850 (7.87)
Renovascular n (%)		
Kidney disease	89 (0.90)	1030 (9.54)
Acute Renal Impairment/failure	37 (0.37)	68 (0.63)
Edema	1779 (17.96)	1905 (17.64)
Congestive Heart Failure n (%)		
Heart failure or Left Ventricular Dysfunction	272 (2.75)	175 (1.62)
Cardiac n (%)		
Myocardial Infarction	444 (4.48)	393 (3.64)
Unstable Angina Pectoris	1054 (10.64)	762 (7.05)
Other (subacute) heart disease	1260 (12.72)	945 (8.75)
Cerebrovascular n (%)		
Intracerebral / Subdural haemorrhage	11 (0.11)	21 (0.19)
Cerebral infarction	48 (0.48)	66 (0.61)
Cerebrovascular accident NOS[#]	143 (1.44)	159 (1.47)
Transient ischemic attack	355 (3.58)	303 (2.81)
Peripheral Arterial Disease n (%)		
Arterial embolism and thrombosis	19 (0.19)	15 (0.14)
Intermittent claudication	172 (1.74)	147 (1.36)
Peripheral vascular disease NOS[#]	192 (1.94)	128 (1.19)
Deep venous thrombosis n (%)		
Deep Venous Thrombosis	435 (4.39)	521 (4.82)
Pulmonary Embolism n (%)		
Pulmonary Embolism	116 (1.17)	141 (1.31)
Hypertension n (%)		
Hypertension	3584 (36.18)	4114 (38.09)
Dyslipidemia n (%)		
Dyslipidemia	1139 (11.50)	1763 (16.32)
Diabetes Mellitus n (%)		
Diabetes diagnostic code	746 (7.53)	959 (8.88)
Insulin prescription	153 (1.54)	197 (1.82)
Oral antidiabetic agent prescription	473 (4.77)	664 (6.15)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

[#] NOS=Not otherwise specified

For OA, 90 and 120 mg will be considered higher than indicated; for RA, 120 mg will be considered higher than indicated

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Table 4HD
Baseline Medications, by Calendar Time Sub-cohort
Higher than indicated doses in OA and RA

Medication	Sub-cohort 1† (N=5027)	Sub-cohort 2‡ (N=5312)
Musculoskeletal and Joint Diseases n (%)		
Other Coxibs	1842 (36.64)	443 (8.34)
Other NSAIDs regarded as Cox-2 selective	384 (7.64)	497 (9.36)
Non-selective NSAIDs	2057 (40.92)	2629 (49.49)
Aspirin	63 (1.25)	24 (0.45)
Paracetamol	2846 (56.61)	2895 (54.50)
DMARDS	110 (2.19)	141 (2.65)
Gout medications	68 (1.35)	36 (0.68)
Oral Corticosteroids	371 (7.38)	546 (10.28)
Local Corticosteroids	297 (5.91)	385 (7.25)
Gastrointestinal Medications n (%)		
Antacids	44 (0.88)	40 (0.75)
H2-receptor antagonists	372 (7.40)	226 (4.25)
Prostaglandin analogues	243 (4.83)	281 (5.29)
Proton pump inhibitors	1323 (26.32)	2011 (37.86)
Cardiovascular Medications n (%)		
Cardiac glycosides	56 (1.11)	47 (0.88)
Diuretics	1014 (20.17)	961 (18.09)
Beta Blocker	877 (17.45)	749 (14.10)
ACE inhibitors	667 (13.27)	906 (17.06)
Angiotensin-II receptor	324 (6.45)	529 (9.96)
Nitrates	387 (7.70)	286 (5.38)
Calcium-channel blockers	759 (15.10)	844 (15.89)
Oral Anticoagulants	67 (1.33)	66 (1.24)
Oral antiplatelet drugs	1005 (19.99)	999 (18.81)
Anion-exchange resins	9 (0.18)	8 (0.15)
Ezetimibe	10 (0.20)	113 (2.13)
Fibrates	44 (0.88)	38 (0.72)
Statins	929 (18.48)	1463 (27.54)
Nicotinic acid	0 (0.00)	4 (0.08)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

For OA, 90 and 120 mg will be considered higher than indicated; for RA, 120 mg will be considered higher than indicated

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Table 4SD
Baseline Medications, by Calendar Time Sub-cohort
Standard doses in OA and RA

Medication	Sub-cohort 1† (N=9906)	Sub-cohort 2‡ (N=10801)
Musculoskeletal and Joint Diseases n (%)		
Other Coxibs	3641 (36.76)	907 (8.40)
Other NSAIDs regarded as Cox-2 selective	745 (7.52)	982 (9.09)
Non-selective NSAIDs	3738 (37.73)	5129 (47.49)
Aspirin	109 (1.10)	35 (0.32)
Paracetamol	5919 (59.75)	6444 (59.66)
DMARDS	599 (6.05)	693 (6.42)
Gout medications	78 (0.79)	80 (0.74)
Oral Corticosteroids	963 (9.72)	1168 (10.81)
Local Corticosteroids	510 (5.15)	761 (7.05)
Gastrointestinal Medications n (%)		
Antacids	113 (1.14)	79 (0.73)
H2-receptor antagonists	812 (8.20)	556 (5.15)
Prostaglandin analogues	547 (5.52)	620 (5.74)
Proton pump inhibitors	2786 (28.12)	4617 (42.75)
Cardiovascular Medications n (%)		
Cardiac glycosides	118 (1.19)	106 (0.98)
Diuretics	2164 (21.85)	2032 (18.81)
Beta Blocker	1755 (17.72)	1688 (15.63)
ACE inhibitors	1317 (13.29)	1772 (16.41)
Angiotensin-II receptor	622 (6.28)	1030 (9.54)
Nitrates	868 (8.76)	638 (5.91)
Calcium-channel blockers	1507 (15.21)	1666 (15.42)
Oral Anticoagulants	119 (1.20)	127 (1.18)
Oral antiplatelet drugs	2096 (21.16)	2158 (19.98)
Anion-exchange resins	11 (0.11)	19 (0.18)
Ezetimibe	21 (0.21)	229 (2.12)
Fibrates	61 (0.62)	83 (0.77)
Statins	1731 (17.47)	2994 (27.72)
Nicotinic acid	3 (0.03)	3 (0.03)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

For OA, 90 and 120 mg will be considered higher than indicated; for RA, 120 mg will be considered higher than indicated

Table 7HD/SD
Etoricoxib Prescribing over a 1-year Period of Follow-up
Median Number of Therapy Days, by Inferred Indication

Inferred Indication	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] (N=45934)
Osteoarthritis (OA)	56.00	42.00
Higher than indicated doses in OA	56.00	28.00
Standard doses in OA	56.00	56.00
Rheumatoid arthritis (RA)	112.00	84.00
Higher than indicated doses in RA	84.00	28.00
Standard doses in RA	112.00	84.00

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

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Table 14HD
Incidence Rate of Clinical Outcomes
First Year Follow-up and First Course Exposure
Higher than indicated doses in OA and RA
Patients without Prior Events

Outcome	Sub-cohort 1†		Sub-cohort 2‡	
	n/N	Incident Rate†† (95% CI)	n/N	Incident Rate†† (95% CI)
Gastrointestinal (GI)				
Gastrointestinal Disease	13/4678	10.43 (5.55, 17.83)	12/4981	10.86 (5.61, 18.96)
Gastrointestinal Medication	15/2045	27.42 (15.35, 45.23)	22/1692	61.77 (38.71, 93.52)
Renovascular				
Edema	30/4182	27.06 (18.25, 38.62)	25/4530	25.07 (16.23, 37.02)
Renal Impairment/Failure	4/5015	2.99 (0.81, 7.65)	3/5284	2.57 (0.53, 7.51)
Congestive Heart Failure				
Heart failure/Left ventricular dysfunction	3/4905	2.29 (0.47, 6.69)	3/5227	2.59 (0.54, 7.58)
Acute Vascular Events				
Cardiovascular System Event	19/4423	16.16 (9.73, 25.24)	15/4740	14.15 (7.92, 23.34)
Coronary Heart Disease	9/4814	7.01 (3.20, 13.30)	2/5113	1.76 (0.21, 6.34)
Acute Myocardial Infarction	9/4856	6.95 (3.18, 13.19)	2/5158	1.75 (0.21, 6.31)
Unstable angina pectoris	0/4961	0.00 (n/a, n/a)	0/5243	0.00 (n/a, n/a)
Cerebrovascular Event	7/4801	5.48 (2.20, 11.28)	9/5116	7.93 (3.63, 15.06)
Intracerebral Haemorrhage	1/5021	0.75 (0.02, 4.16)	0/5307	0.00 (n/a, n/a)
Cerebral Infarction	0/5001	0.00 (n/a, n/a)	4/5286	3.43 (0.93, 8.78)
Cerebrovascular Accident NOS‡‡	2/4944	1.51 (0.18, 5.46)	2/5246	1.72 (0.21, 6.21)
Transient Ischemic Attack	6/4880	4.63 (1.70, 10.08)	6/5176	5.25 (1.93, 11.42)
Arterial embolism / thrombosis	1/5022	0.75 (0.02, 4.15)	0/5310	0.00 (n/a, n/a)
Deep Venous Thrombosis	6/4840	4.63 (1.70, 10.08)	5/5125	4.42 (1.44, 10.33)
Pulmonary Embolism	2/4968	1.51 (0.18, 5.46)	3/5255	2.59 (0.53, 7.56)
Sudden/unexplained death				
Sudden/unexplained death	1/5021	0.75 (0.02, 4.16)	0/5306	0.00 (n/a, n/a)
Acute Vascular event or sudden death				
Any acute vascular event or sudden/unexplained death	20/4420	17.05 (10.41, 26.32)	15/4735	14.16 (7.92, 23.35)
Hypertension				
Diagnosis only	46/3436	52.72 (38.60, 70.32)	37/3539	48.46 (34.12, 66.80)
Diagnosis + medication	31/4222	28.20 (19.16, 40.03)	24/4383	25.12 (16.10, 37.38)
Cardiovascular medication				
Cardiovascular medication	4/1884	8.41 (2.29, 21.54)	11/1896	27.35 (13.65, 48.93)
Blood Pressure				
Blood Pressure Measurement	1/130	27.55 (0.70, 153.47)	0/58	0.00 (n/a, n/a)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

NOS=Not otherwise specified

†† Per 1000 person year

For OA, 90 and 120 mg will be considered higher than indicated; for RA, 120 mg will be considered higher than indicated

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Table 14SD
Incidence Rate of Clinical Outcomes
First Year Follow-up and First Course Exposure
Standard doses in OA and RA
Patients without Prior Events

Outcome	Sub-cohort 1†		Sub-cohort 2‡	
	n/N	Incident Rate†† (95% CI)	n/N	Incident Rate†† (95% CI)
Gastrointestinal (GI)				
Gastrointestinal Disease	25/9176	9.27 (6.00, 13.68)	10/9998	3.90 (1.87, 7.18)
Gastrointestinal Medication	32/3816	28.71 (19.63, 40.52)	35/2855	48.31 (33.65, 67.19)
Renovascular				
Edema	44/8128	18.58 (13.50, 24.94)	57/8896	25.16 (19.05, 32.59)
Renal Impairment/Failure	8/9869	2.75 (1.19, 5.42)	6/10733	2.18 (0.80, 4.74)
Congestive Heart Failure				
Heart failure/Left ventricular dysfunction	11/9640	3.86 (1.93, 6.91)	8/10632	2.92 (1.26, 5.76)
Acute Vascular Events				
Cardiovascular System Event	37/8701	14.45 (10.17, 19.91)	33/9588	13.28 (9.14, 18.65)
Coronary Heart Disease	14/9470	5.03 (2.75, 8.44)	8/10417	2.97 (1.28, 5.86)
Acute Myocardial Infarction	10/9579	3.55 (1.70, 6.53)	8/10491	2.96 (1.28, 5.82)
Unstable angina pectoris	7/9744	2.44 (0.98, 5.04)	0/10682	0.00 (n/a, n/a)
Cerebrovascular Event	18/9451	6.46 (3.83, 10.22)	17/10365	6.37 (3.71, 10.20)
Intracerebral Haemorrhage	1/9895	0.34 (0.01, 1.91)	1/10780	0.36 (0.01, 2.01)
Cerebral Infarction	6/9859	2.07 (0.76, 4.50)	4/10736	1.45 (0.40, 3.72)
Cerebrovascular Accident NOS‡‡	8/9763	2.78 (1.20, 5.49)	10/10642	3.66 (1.76, 6.73)
Transient Ischemic Attack	9/9576	3.18 (1.46, 6.04)	8/10528	2.95 (1.27, 5.81)
Arterial embolism / thrombosis	0/9894	0.00 (n/a, n/a)	0/10789	0.00 (n/a, n/a)
Deep Venous Thrombosis	9/9569	3.19 (1.46, 6.06)	12/10428	4.47 (2.31, 7.81)
Pulmonary Embolism	2/9794	0.69 (0.08, 2.50)	4/10666	1.46 (0.40, 3.74)
Sudden/unexplained death				
Sudden/unexplained death	1/9875	0.34 (0.01, 1.92)	0/10777	0.00 (n/a, n/a)
Acute Vascular event or sudden death				
Any acute vascular event or sudden/unexplained death	37/8673	14.50 (10.21, 19.98)	33/9566	13.31 (9.16, 18.70)
Hypertension				
Diagnosis only	101/6585	54.20 (44.15, 65.86)	70/6977	39.97 (31.16, 50.50)
Diagnosis + medication	73/8239	30.69 (24.06, 38.59)	50/8800	22.42 (16.64, 29.55)
Cardiovascular medication				
Cardiovascular medication	11/3537	10.81 (5.40, 19.34)	14/3631	14.95 (8.17, 25.09)
Blood Pressure				
Blood Pressure Measurement	3/266	39.25 (8.09, 114.69)	1/56	57.35 (1.45, 319.56)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013

NOS=Not otherwise specified

†† Per 1000 person year

For OA, 90 and 120 mg will be considered higher than indicated; for RA, 120 mg will be considered higher than indicated

10.5.2 Description of Analysis of potential time trends

For the analyses of patient characteristics and clinical outcomes by calendar time (CT) sub-cohorts, the period since marketing approval was divided into 4 time frames. The Sub-cohort 1 time period from 01Apr02 through 17Feb05 was maintained as is. The Sub-cohort 2 time period from 18Feb05 through 30June13 was divided into 3 time frames: Sub-cohort 2a: 18Feb05 – 31Dec07, Sub-cohort 2b: 01Jan08 – 31Dec10, and Sub-cohort 2c: 01Jan11 – 30Jun13.

Table 1CT provides the baseline characteristics (demographics and indications) for the 4 time periods of interest. It should be noted that the population in the third interval for Sub-cohort 2 was much smaller than the prior two intervals. This is a function primarily of a decrease in new prescribing as well as a slightly shorter interval. The proportion of men appears to have increased slightly over time (from 39.5% for Sub-cohort 1 to 45.1% for Sub-cohort 2c), while the mean age decreased slightly over time (from 60.7% for Sub-cohort 1 to 57.2% for Sub-cohort 2c). The proportion of subjects with an OA indication decreased over time while the proportions of subjects with gouty arthritis and none of the labelled indications ("off label" use) increased over time.

Table 2CT shows that the proportion of active smokers remained very stable over time (~21%), while the mean SBP and DBP decreased slightly over time. **Table 3CT** provides the baseline medical history over time. The proportion of patients with a baseline history of most medical conditions jumped up and down slightly over time. The proportion of patients with a history of cardiac or cerebrovascular events or CHF showed a slight decline over time while the proportion with a history of diabetes increased slightly over time. The proportion with a history of a GI event is fairly steady over time. The proportion of patients with kidney disease varied substantially between Sub-cohort 1 and Sub-cohort 2. This was likely the result of a change in the READ codes over time or potential increases in reporting rates (e.g., due to NHS policies) rather than a real difference in the baseline rates of kidney disease.

Table 4CT provides data on baseline medication use over time. There number of patients with baseline use of several types of medications increased slightly over time: non-selective NSAIDs, DMARDS, gout medications, oral corticosteroids, local corticosteroids, ACE inhibitors, angiotensin receptor blockers, and ezetimibe. The largest increases were in use of proton pump inhibitors and statins. The number of patients with baseline use of several types of medications also decreased slightly over time: other Coxibs, H2 receptor antagonists, prostaglandin analogues, cardiac glycosides, diuretics, beta blockers, nitrates, and oral antiplatelets.

The distribution of initial etoricoxib doses is provided in **Table 5CT.** Because the 30 mg dose was not introduced until 2007, none of the patients in Sub-cohort 1 or in the first interval for Sub-cohort 2 used this dose. After the introduction of the 30 mg dose, the use of 30 mg increased and the use of 60 mg decreased over time for the All Ages group. The use of 90 and 120 mg doses has shown some variation over time. The patterns were generally similar for the <65 and ≥65 age group, with some

variation in the last time interval which included fewer patients. The distribution of initial doses by indication is shown in **Table 6CT.** In general, the pattern was similar to the overall group in **Table 5CT.**

Tables 7CT, 8CT, and 9CT provide data on the median number of therapy days by inferred indication (7CT), gender and age (8CT), and initial dose (9CT). For most indications, the overall trend was for a decrease in the median number of days between Sub-cohort 1 and the third time interval for Sub-cohort 2 with some variability in between. While the mean and median number of days of therapy is generally higher in women, there is a trend toward a decreased duration of therapy over time for both genders. In Sub-cohort 1, the over age 65 group had a slightly higher mean and median number of days of etoricoxib therapy in Sub-cohort 1, but since that time, the mean and median number of days of therapy has stayed steady or declined for both age groups, and the older group has had slightly fewer days of therapy in the last 2 time intervals of Sub-cohort 2 than earlier periods. Overall, the mean and median number of days of etoricoxib therapy have tended to decrease or stay steady over time for all initial dose groups.

Tables 10CT, 11CT, and 12CT provide data on the median medication possession ratio. In general, across inferred indication (10CT), initial dose (11CT), and age and gender (12CT), the median medication possession ratio tended to remain steady or decrease slightly over time.

Changes in etoricoxib dose and switches to other NSAIDS are described in **Table 13CT.** The proportion increasing or decreasing their etoricoxib dose remained under 5% over time. The proportion switching to other NSAIDs increased very slightly over time (from 29.1% for Sub-cohort 1 to 32.5% for the most recent time interval for Sub-cohort 2).

Table 14CT provides data on the incidence rate of clinical outcomes during the first year of follow-up and first course exposure in patients without a history of each specific outcome. There was no consistent trend for an increase in any of the clinical outcomes over time (except for use of GI medications and blood pressure measurements which are positive trends). There did appear to be a trend for a decreasing incidence of hypertension over time. For most of the clinical outcomes, the incidence rates showed moderate variability (with overlapping confidence intervals) over time which appeared to be due in large part to the small numbers of events in the 3 time intervals for Sub-cohort 2.

Tables 15CT and 16CT provide similar data to Table 14CT; however, for **Table 15CT**, exposure was truncated when another NSAID prescription was written and for **Table 16CT**, exposure was truncated when another NSAID prescription was written and patients with a prior event were included. The results are generally similar to Table 14CT; however, the data were even more variable due to smaller numbers of cases for some clinical outcomes.

Table 1CT
Baseline Demographics and Indication for Etoricoxib, by Calendar Time Sub-cohort

Characteristic	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡]		
		Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Indication for etoricoxib use n (%)				
Osteoarthritis	13752 (41.35)	6415 (34.48)	6064 (32.00)	2199 (26.24)
Rheumatoid arthritis	1181 (3.55)	574 (3.09)	564 (2.98)	297 (3.54)
Gouty arthritis	2877 (8.65)	2421 (13.01)	2417 (12.75)	1367 (16.31)
Ankylosing spondylitis (AS)	286 (0.86)	189 (1.02)	237 (1.25)	171 (2.04)
More than one OA RA Gout or AS diagnoses	2278 (6.85)	1036 (5.57)	1061 (5.60)	421 (5.02)
Arthritis NOS[#]	1709 (5.14)	924 (4.97)	994 (5.25)	477 (5.69)
None of the Above Indications	11172 (33.59)	7044 (37.86)	7614 (40.18)	3448 (41.15)
Gender n (%)				
Male	13136 (39.50)	7889 (42.41)	8079 (42.63)	3780 (45.11)
Female	20119 (60.50)	10713 (57.59)	10872 (57.37)	4600 (54.89)
Indeterminate	0 (0.00)	1 (0.01)	0 (0.00)	0 (0.00)
Age (years)				
N	33255	18603	18951	8380
Mean	60.70	58.28	57.85	57.18
Std. Deviation	15.80	15.98	15.85	15.85
Minimum	12.73	2.81	11.86	11.65
25th Percentile	49.76	46.68	46.55	46.07
Median	61.34	58.88	57.97	56.89
75th Percentile	72.81	70.17	69.28	68.60
Maximum	104.76	101.57	103.63	101.27
Age<65 Years n (%)	19337 (58.15)	12091 (64.99)	12475 (65.83)	5629 (67.17)
Age>=65 Years n (%)	13918 (41.85)	6512 (35.01)	6476 (34.17)	2751 (32.83)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods: Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

[#] NOS=Not otherwise specified as OA, RA, AS, or Gout

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Table 2CT
Baseline Cardiovascular Risk Factors by Calendar Time Sub-cohort

Characteristic	Sub-cohort 1† (N=33255)	Sub-cohort 2‡ Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Smoking Status n (%)				
Missing	2605 (7.83)	429 (2.31)	129 (0.68)	23 (0.27)
Ex-Smoker	7235 (21.76)	4734 (25.45)	5105 (26.94)	2382 (28.42)
Non-Smoker	16129 (48.50)	9475 (50.93)	9715 (51.26)	4267 (50.92)
Smoker	7286 (21.91)	3965 (21.31)	4002 (21.12)	1708 (20.38)
Body Mass Index(kg/m2)				
N	27641	16233	17293	7695
Mean	27.66	27.92	28.29	28.53
Std. Deviation	5.38	5.56	5.69	5.73
Minimum	15.00	15.00	15.00	15.00
25th Percentile	23.90	24.10	24.30	24.60
Median	26.90	27.10	27.50	27.70
75th Percentile	30.50	30.90	31.50	31.70
Maximum	54.00	54.00	53.90	53.60
< 20 n (%)	1068 (3.21)	638 (3.43)	637 (3.36)	257 (3.07)
20-24 n (%)	8224 (24.73)	4600 (24.73)	4556 (24.04)	1868 (22.29)
25-29 n (%)	10593 (31.85)	6089 (32.73)	6349 (33.50)	2922 (34.87)
>= 30 n (%)	7756 (23.32)	4906 (26.37)	5751 (30.35)	2648 (31.60)
Missing n (%)	5614 (16.88)	2370 (12.74)	1658 (8.75)	685 (8.17)
Systolic Blood Pressure (mmHg)				
N	31736	18062	18563	8198
Mean	136.05	132.76	131.56	130.80
Std. Deviation	18.69	16.59	15.99	15.83
Minimum	63.00	70.00	78.00	70.00
25th Percentile	121.00	120.00	120.00	120.00
Median	136.00	132.00	130.00	130.00
75th Percentile	148.00	142.00	140.00	140.00
Maximum	266.00	227.00	228.00	223.00
< 140 n (%)	16915 (50.86)	11150 (59.94)	12374 (65.29)	5650 (67.42)
140-149 n (%)	7365 (22.15)	4281 (23.01)	4058 (21.41)	1686 (20.12)
150-159 n (%)	3758 (11.30)	1506 (8.10)	1211 (6.39)	509 (6.07)
>= 160 n (%)	3698 (11.12)	1125 (6.05)	920 (4.85)	353 (4.21)
Missing n (%)	1519 (4.57)	541 (2.91)	388 (2.05)	182 (2.17)

Characteristic	Sub-cohort 1† (N=33255)	Sub-cohort 2‡		
		Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Diastolic Blood Pressure (mmHg)				
N	31638	18029	18560	8198
Mean	79.55	78.54	77.98	77.90
Std. Deviation	9.71	9.48	9.49	9.69
Minimum	40.00	40.00	40.00	42.00
25th Percentile	72.00	70.00	70.00	70.00
Median	80.00	80.00	80.00	80.00
75th Percentile	85.00	84.00	84.00	84.00
Maximum	138.00	130.00	140.00	130.00
< 90 n (%)	26361 (79.27)	15682 (84.30)	16472 (86.92)	7267 (86.72)
>=90 n (%)	5277 (15.87)	2347 (12.62)	2088 (11.02)	931 (11.11)
Missing n (%)	1617 (4.86)	574 (3.09)	391 (2.06)	182 (2.17)
Number of Blood Pressure Measurements in prior 6 months				
N	14469	8299	8649	3728
Mean	1.96	1.85	1.81	1.75
Std. Deviation	1.67	1.49	1.55	1.45
Minimum	1.00	1.00	1.00	1.00
25th Percentile	1.00	1.00	1.00	1.00
Median	1.00	1.00	1.00	1.00
75th Percentile	2.00	2.00	2.00	2.00
Maximum	33.00	17.00	28.00	21.00
Missing n (%)	18786 (56.49)	10304 (55.39)	10302 (54.36)	4652 (55.51)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods:
Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

Table 3CT
Baseline Medical History by Calendar Time Sub-cohort

Medical History	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡] Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Gastrointestinal n (%)				
Gastrointestinal Ulcer, Perforation/Bleeding	2218 (6.67)	1162 (6.25)	1105 (5.83)	512 (6.11)
Renovascular n (%)				
Kidney disease	345 (1.04)	950 (5.11)	1941 (10.24)	888 (10.60)
Acute Renal Impairment/failure	145 (0.44)	112 (0.60)	112 (0.59)	51 (0.61)
Edema	4524 (13.60)	2359 (12.68)	2395 (12.64)	1040 (12.41)
Congestive Heart Failure n (%)				
Heart failure or Left Ventricular Dysfunction	883 (2.66)	347 (1.87)	286 (1.51)	125 (1.49)
Cardiac n (%)				
Myocardial Infarction	1516 (4.56)	668 (3.59)	594 (3.13)	282 (3.37)
Unstable Angina Pectoris	2899 (8.72)	1162 (6.25)	1005 (5.30)	371 (4.43)
Other (subacute) heart disease	3631 (10.92)	1464 (7.87)	1283 (6.77)	514 (6.13)
Cerebrovascular n (%)				
Intracerebral / Subdural haemorrhage	46 (0.14)	17 (0.09)	28 (0.15)	14 (0.17)
Cerebral infarction	163 (0.49)	78 (0.42)	107 (0.56)	50 (0.60)
Cerebrovascular accident NOS[#]	478 (1.44)	208 (1.12)	220 (1.16)	94 (1.12)
Transient ischemic attack	923 (2.78)	412 (2.21)	444 (2.34)	183 (2.18)
Peripheral Arterial Disease n (%)				
Arterial embolism and thrombosis	63 (0.19)	15 (0.08)	22 (0.12)	7 (0.08)
Intermittent claudication	519 (1.56)	208 (1.12)	211 (1.11)	95 (1.13)
Peripheral vascular disease NOS[#]	514 (1.55)	203 (1.09)	182 (0.96)	88 (1.05)
Deep venous thrombosis n (%)				
Deep Venous Thrombosis	1215 (3.65)	609 (3.27)	654 (3.45)	352 (4.20)
Pulmonary Embolism n (%)				
Pulmonary Embolism	318 (0.96)	174 (0.94)	200 (1.06)	96 (1.15)
Hypertension n (%)				
Hypertension	10372 (31.19)	5642 (30.33)	6045 (31.90)	2632 (31.41)
Dyslipidemia n (%)				
Dyslipidemia	3421 (10.29)	2150 (11.56)	2583 (13.63)	1215 (14.50)
Diabetes Mellitus n (%)				
Diabetes diagnostic code	2464 (7.41)	1365 (7.34)	1597 (8.43)	758 (9.05)
Insulin prescription	560 (1.68)	292 (1.57)	331 (1.75)	131 (1.56)
Oral antidiabetic agent prescription	1527 (4.59)	887 (4.77)	1100 (5.80)	519 (6.19)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods: Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

[#] NOS=Not otherwise specified

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Table 4CT
Baseline Medications, by Calendar Time Sub-cohort

Medication	Sub-cohort 1† (N=33255)	Sub-cohort 2‡		
		Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Musculoskeletal and Joint Diseases n (%)				
Other Coxibs	9620 (28.93)	1649 (8.86)	658 (3.47)	223 (2.66)
Other NSAIDs regarded as Cox-2 selective	1954 (5.88)	1389 (7.47)	1191 (6.28)	429 (5.12)
Non-selective NSAIDs	12484 (37.54)	8225 (44.21)	8543 (45.08)	4045 (48.27)
Aspirin	359 (1.08)	74 (0.40)	76 (0.40)	32 (0.38)
Paracetamol	16312 (49.05)	8455 (45.45)	8813 (46.50)	3973 (47.41)
DMARDS	1287 (3.87)	589 (3.17)	671 (3.54)	383 (4.57)
Gout medications	1111 (3.34)	696 (3.74)	772 (4.07)	498 (5.94)
Oral Corticosteroids	2559 (7.70)	1413 (7.60)	1710 (9.02)	849 (10.13)
Local Corticosteroids	1380 (4.15)	888 (4.77)	957 (5.05)	469 (5.60)
Gastrointestinal Medications n (%)				
Antacids	298 (0.90)	131 (0.70)	96 (0.51)	37 (0.44)
H2-receptor antagonists	2358 (7.09)	862 (4.63)	661 (3.49)	258 (3.08)
Prostaglandin analogues	1386 (4.17)	1048 (5.63)	624 (3.29)	130 (1.55)
Proton pump inhibitors	8022 (24.12)	5378 (28.91)	6873 (36.27)	3654 (43.60)
Cardiovascular Medications n (%)				
Cardiac glycosides	469 (1.41)	217 (1.17)	170 (0.90)	59 (0.70)
Diuretics	6026 (18.12)	2983 (16.04)	2683 (14.16)	1008 (12.03)
Beta Blocker	5523 (16.61)	2733 (14.69)	2579 (13.61)	1120 (13.37)
ACE inhibitors	4265 (12.83)	2497 (13.42)	2994 (15.80)	1316 (15.70)
Angiotensin-II receptor	1902 (5.72)	1346 (7.24)	1666 (8.79)	706 (8.42)
Nitrates	2438 (7.33)	919 (4.94)	868 (4.58)	333 (3.97)
Calcium-channel blockers	4362 (13.12)	2311 (12.42)	2543 (13.42)	1093 (13.04)
Oral Anticoagulants	484 (1.46)	260 (1.40)	275 (1.45)	128 (1.53)
Oral antiplatelet drugs	6120 (18.40)	2991 (16.08)	3124 (16.48)	1208 (14.42)
Anion-exchange resins	40 (0.12)	19 (0.10)	33 (0.17)	13 (0.16)
Ezetimibe	59 (0.18)	241 (1.30)	390 (2.06)	148 (1.77)
Fibrates	255 (0.77)	125 (0.67)	126 (0.66)	67 (0.80)
Statins	5414 (16.28)	3785 (20.35)	4636 (24.46)	2036 (24.30)
Nicotinic acid	4 (0.01)	11 (0.06)	9 (0.05)	2 (0.02)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods:
Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

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Table 5CT
Distribution of Initial Etoricoxib Dose by Age and Calendar Time Sub-cohort

Initial Etoricoxib Dose	Sub-cohort 1† (N=33255)	Sub-cohort 2‡		
		Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
All Ages				
N	33255	18603	18951	8380
30 mg	0 (0.00)	0 (0.00)	3030 (15.99)	1407 (16.79)
60 mg	18787 (56.49)	9353 (50.28)	7600 (40.10)	2884 (34.42)
90 mg	9165 (27.56)	5576 (29.97)	5144 (27.14)	2307 (27.53)
120 mg	5303 (15.95)	3674 (19.75)	3177 (16.76)	1782 (21.26)
Age < 65				
N	19337	12091	12475	5629
30 mg	0 (0.00)	0 (0.00)	1717 (13.76)	881 (15.65)
60 mg	9992 (51.67)	5664 (46.84)	4930 (39.52)	1928 (34.25)
90 mg	5835 (30.18)	3925 (32.46)	3710 (29.74)	1681 (29.86)
120 mg	3510 (18.15)	2502 (20.69)	2118 (16.98)	1139 (20.23)
Age >= 65				
N	13918	6512	6476	2751
30 mg	0 (0.00)	0 (0.00)	1313 (20.27)	526 (19.12)
60 mg	8795 (63.19)	3689 (56.65)	2670 (41.23)	956 (34.75)
90 mg	3330 (23.93)	1651 (25.35)	1434 (22.14)	626 (22.76)
120 mg	1793 (12.88)	1172 (18.00)	1059 (16.35)	643 (23.37)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods:
Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

Table 6CT
Distribution of Initial Etoricoxib Dose by Indication

Indication	Sub-cohort 1[†] (N=33255) n (%)	Sub-cohort 2[‡] Sub-cohort 2a (N=18603) n (%)	Sub-cohort 2b (N=18951) n (%)	Sub-cohort 2c (N=8380) n (%)
Osteoarthritis (OA)				
30 mg	0 (0.00)	0 (0.00)	1293 (21.32)	534 (24.28)
60 mg	8822 (64.15)	3870 (60.33)	2865 (47.25)	933 (42.43)
90 mg	3616 (26.29)	1909 (29.76)	1499 (24.72)	558 (25.38)
120 mg	1314 (9.55)	636 (9.91)	407 (6.71)	174 (7.91)
Rheumatoid Arthritis (RA)				
30 mg	0 (0.00)	0 (0.00)	65 (11.52)	44 (14.81)
60 mg	480 (40.64)	223 (38.85)	173 (30.67)	92 (30.98)
90 mg	604 (51.14)	288 (50.17)	286 (50.71)	135 (45.45)
120 mg	97 (8.21)	63 (10.98)	40 (7.09)	26 (8.75)
Gout				
30 mg	0 (0.00)	0 (0.00)	141 (5.83)	54 (3.95)
60 mg	941 (32.71)	576 (23.79)	428 (17.71)	187 (13.68)
90 mg	462 (16.06)	334 (13.80)	373 (15.43)	162 (11.85)
120 mg	1474 (51.23)	1511 (62.41)	1475 (61.03)	964 (70.52)
Ankylosing spondylitis (AS)				
30 mg	0 (0.00)	0 (0.00)	21 (8.86)	10 (5.85)
60 mg	108 (37.76)	70 (37.04)	58 (24.47)	33 (19.30)
90 mg	143 (50.00)	102 (53.97)	141 (59.49)	122 (71.35)
120 mg	35 (12.24)	17 (8.99)	17 (7.17)	6 (3.51)
More than one OA RA Gout or AS diagnoses				
30 mg	0 (0.00)	0 (0.00)	173 (16.31)	75 (17.81)
60 mg	1222 (53.64)	498 (48.07)	379 (35.72)	135 (32.07)
90 mg	703 (30.86)	338 (32.63)	307 (28.93)	117 (27.79)
120 mg	353 (15.50)	200 (19.31)	202 (19.04)	94 (22.33)
Arthritis NOS[#]				
30 mg	0 (0.00)	0 (0.00)	141 (14.19)	81 (16.98)
60 mg	944 (55.24)	509 (55.09)	414 (41.65)	145 (30.40)
90 mg	572 (33.47)	315 (34.09)	351 (35.31)	194 (40.67)
120 mg	193 (11.29)	100 (10.82)	88 (8.85)	57 (11.95)
None of the Above Indications				
30 mg	0 (0.00)	0 (0.00)	1196 (15.71)	609 (17.66)
60 mg	6270 (56.12)	3607 (51.21)	3283 (43.12)	1359 (39.41)
90 mg	3065 (27.43)	2290 (32.51)	2187 (28.72)	1019 (29.55)
120 mg	1837 (16.44)	1147 (16.28)	948 (12.45)	461 (13.37)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods: Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

[#] NOS=Not otherwise specified

Table 7CT
Etoricoxib Prescribing over a 1-year Period of Follow-up
Median Number of Therapy Days, by Inferred Indication

Inferred Indication	Sub-cohort 1[†] (N=33255)	Sub-cohort 2[‡]		
		Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Osteoarthritis (OA)	56.00	42.00	44.50	28.00
Rheumatoid arthritis (RA)	112.00	70.00	84.00	56.00
Gout	28.00	21.00	21.00	14.00
Ankylosing spondylitis (AS)	166.00	112.00	140.00	140.00
More than one OA RA Gout or AS diagnoses	56.00	40.50	28.00	28.00
Arthritis NOS[#]	56.00	56.00	30.00	56.00
None of the Above Indications	28.00	28.00	28.00	28.00

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods: Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

[#] NOS=Not otherwise specified

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Table 8CT
Etoricoxib Prescribing over a 1-year Period of Follow-up
Number of Days of Therapy
Stratified by Gender and by Age Group

	Sub-cohort 1[†]	Sub-cohort 2[‡]		
	(N=33255)	Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Men				
N	13136	7889	8079	3780
Mean	89.30	70.72	73.50	65.20
Std. Deviation	103.29	90.84	94.44	79.95
Minimum	2.00	1.00	1.00	3.00
25th Percentile	28.00	28.00	28.00	28.00
Median	30.00	28.00	28.00	28.00
75th Percentile	112.00	70.00	84.00	56.00
Maximum	365.00	365.00	365.00	365.00
Women				
N	20119	10713	10872	4600
Mean	100.10	83.61	85.10	78.82
Std. Deviation	108.19	99.41	100.90	88.52
Minimum	1.00	1.00	1.00	5.00
25th Percentile	28.00	28.00	28.00	28.00
Median	56.00	28.00	28.00	28.00
75th Percentile	140.00	84.00	91.00	84.00
Maximum	365.00	365.00	365.00	365.00
Age < 65 Years				
N	19337	12091	12475	5629
Mean	92.16	77.49	80.90	75.02
Std. Deviation	104.36	94.82	98.17	86.25
Minimum	1.00	1.00	1.00	3.00
25th Percentile	28.00	28.00	28.00	28.00
Median	30.00	28.00	28.00	28.00
75th Percentile	112.00	84.00	84.00	84.00
Maximum	365.00	365.00	365.00	365.00
Age >=65 Years				
N	13918	6512	6476	2751
Mean	100.93	79.34	78.72	67.88
Std. Deviation	109.00	98.36	98.71	82.28
Minimum	1.00	3.00	1.00	3.00
25th Percentile	28.00	28.00	28.00	28.00
Median	56.00	28.00	28.00	28.00
75th Percentile	140.00	84.00	84.00	70.00
Maximum	365.00	365.00	365.00	365.00

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods: Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

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Table 9CT
Etoricoxib Prescribing over a 1-year Period of Follow-up
Number of Days of Therapy
By Initial Etoricoxib Dose[#]

	Sub-cohort 1[†]	Sub-cohort 2[‡]		
	(N=33255)	Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Etoricoxib 30 mg				
N	0	0	2540	1215
Mean	0.00	0.00	74.98	74.58
Std. Deviation	0.00	0.00	89.99	84.41
Minimum	0.00	0.00	2.00	5.00
25th Percentile	0.00	0.00	28.00	28.00
Median	0.00	0.00	28.00	28.00
75th Percentile	0.00	0.00	80.00	84.00
Maximum	0.00	0.00	365.00	365.00
Etoricoxib 60 mg				
N	16107	8148	6646	2566
Mean	90.23	76.66	77.88	69.63
Std. Deviation	100.32	91.23	92.35	80.30
Minimum	1.00	3.00	1.00	3.00
25th Percentile	28.00	28.00	28.00	28.00
Median	30.00	28.00	28.00	28.00
75th Percentile	112.00	84.00	84.00	84.00
Maximum	365.00	365.00	365.00	365.00
Etoricoxib 90 mg				
N	7383	4636	4439	2046
Mean	96.61	79.51	78.17	74.83
Std. Deviation	106.01	94.88	93.91	84.98
Minimum	1.00	1.00	1.00	7.00
25th Percentile	28.00	28.00	28.00	28.00
Median	35.00	28.00	28.00	28.00
75th Percentile	140.00	84.00	84.00	84.00
Maximum	365.00	365.00	365.00	365.00
Etoricoxib 120 mg				
N	4187	3030	2731	1620
Mean	38.76	27.52	24.32	30.04
Std. Deviation	60.99	44.20	42.24	32.69
Minimum	1.00	1.00	3.00	5.00
25th Percentile	7.00	7.00	7.00	14.00
Median	21.00	14.00	14.00	28.00
75th Percentile	28.00	28.00	28.00	28.00
Maximum	365.00	365.00	364.00	365.00

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods: Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

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Table 10CT
Etoricoxib Prescribing over a 1-year Period of Follow-up
Median Medication Possession Ratio[††] by Inferred Indication

	Sub-cohort 1[†]	Sub-cohort 2[‡]		
	(N=33255)	Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Osteoarthritis (OA)	0.15	0.15	0.15	0.15
Rheumatoid arthritis (RA)	0.31	0.23	0.23	0.23
Gout	0.08	0.08	0.06	0.04
Ankylosing spondylitis (AS)	0.46	0.38	0.38	0.38
More than one OA RA Gout or AS diagnoses	0.15	0.15	0.09	0.15
Arthritis NOS[#]	0.15	0.15	0.12	0.15
None of the Above Indications	0.08	0.08	0.08	0.08

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods:
Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

[#] NOS=Not otherwise specified

[††] Medication Possession Ratio = Proportion of days over one year covered by etoricoxib prescriptions.

Table 11CT
Etoricoxib Prescribing over a 1-year Period of Follow-up
Medication Possession Ratio[††]
By Initial Etoricoxib Dose[#]

	Sub-cohort 1[†]	Sub-cohort 2[‡]		
	(N=33255)	Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Etoricoxib 30 mg				
N	0	0	2540	1215
Mean	0.00	0.00	0.23	0.23
Std. Deviation	0.00	0.00	0.27	0.25
Minimum	0.00	0.00	0.01	0.02
25th Percentile	0.00	0.00	0.08	0.08
Median	0.00	0.00	0.08	0.08
75th Percentile	0.00	0.00	0.23	0.23
Maximum	0.00	0.00	1.00	1.00
Etoricoxib 60 mg				
N	16107	8148	6646	2566
Mean	0.26	0.23	0.23	0.22
Std. Deviation	0.29	0.26	0.27	0.25
Minimum	0.00	0.01	0.01	0.02
25th Percentile	0.08	0.08	0.08	0.08
Median	0.12	0.08	0.08	0.08
75th Percentile	0.33	0.23	0.23	0.23
Maximum	1.00	1.00	1.00	1.00
Etoricoxib 90 mg				
N	7383	4636	4439	2046
Mean	0.28	0.24	0.23	0.23
Std. Deviation	0.30	0.28	0.27	0.25
Minimum	0.00	0.01	0.01	0.02
25th Percentile	0.08	0.08	0.08	0.08
Median	0.15	0.08	0.08	0.08
75th Percentile	0.38	0.30	0.24	0.26
Maximum	1.00	1.00	1.00	1.00
Etoricoxib 120 mg				
N	4187	3030	2731	1620
Mean	0.12	0.09	0.07	0.10
Std. Deviation	0.18	0.14	0.13	0.12
Minimum	0.00	0.00	0.01	0.01
25th Percentile	0.02	0.02	0.02	0.04
Median	0.06	0.04	0.04	0.08
75th Percentile	0.10	0.08	0.08	0.08
Maximum	1.00	1.00	1.00	1.00

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods: Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

[††] Medication Possession Ratio = Proportion of days over one year covered by etoricoxib prescriptions.

[#] Patients prescribed a different dose of etoricoxib following their initial excluded.

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Table 12CT
Etoricoxib Prescribing over a 1-year Period of Follow-up
Medication Possession Ratio††
Stratified by Gender and by Age Group

Characteristic	Sub-cohort 1† (N=33255)	Sub-cohort 2‡		
		Sub-cohort 2a (N=18603)	Sub-cohort 2b (N=18951)	Sub-cohort 2c (N=8380)
Men				
N	13136	7889	8079	3780
Mean	0.26	0.21	0.22	0.20
Std. Deviation	0.29	0.26	0.27	0.24
Minimum	0.01	0.00	0.01	0.01
25th Percentile	0.08	0.08	0.08	0.08
Median	0.10	0.08	0.08	0.08
75th Percentile	0.33	0.23	0.23	0.23
Maximum	1.00	1.00	1.00	1.00
Women				
N	20119	10713	10872	4600
Mean	0.29	0.24	0.25	0.24
Std. Deviation	0.30	0.28	0.29	0.26
Minimum	0.00	0.01	0.01	0.01
25th Percentile	0.08	0.08	0.08	0.08
Median	0.15	0.08	0.08	0.08
75th Percentile	0.42	0.31	0.31	0.31
Maximum	1.00	1.00	1.00	1.00
Age < 65 Years				
N	19337	12091	12475	5629
Mean	0.26	0.22	0.23	0.22
Std. Deviation	0.29	0.27	0.28	0.25
Minimum	0.00	0.00	0.01	0.01
25th Percentile	0.08	0.08	0.08	0.08
Median	0.10	0.08	0.08	0.08
75th Percentile	0.35	0.23	0.27	0.23
Maximum	1.00	1.00	1.00	1.00
Age >=65 Years				
N	13918	6512	6476	2751
Mean	0.29	0.24	0.24	0.22
Std. Deviation	0.31	0.29	0.29	0.26
Minimum	0.00	0.01	0.01	0.01
25th Percentile	0.08	0.08	0.08	0.08
Median	0.15	0.08	0.08	0.08
75th Percentile	0.46	0.27	0.28	0.23
Maximum	1.00	1.00	1.00	1.00

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods:
Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

†† Medication Possession Ratio = Proportion of days over one year covered by etoricoxib prescriptions

Table 13CT
Changes in Etoricoxib Dose or Type of NSAID / Coxib
Over a 1 Year Period of Follow-up

	Sub-cohort 1†	Sub-cohort 2‡		
		Sub-cohort 2a	Sub-cohort 2b	Sub-cohort 2c
	(N=33255)	(N=18603)	(N=18951)	(N=8380)
Indication	n (%)	n (%)	n (%)	n (%)
Dose Increased	1928 (5.80)	751 (4.04)	960 (5.07)	422 (5.04)
Dose Decreased	1240 (3.73)	699 (3.76)	757 (3.99)	363 (4.33)
Switch to other NSAIDS	12363 (37.18)	5906 (31.75)	5936 (31.32)	2723 (32.49)

† First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

‡ First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods: Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

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Table 14CT
Incidence Rate of Clinical Outcomes
First Year Follow-up and First Course Exposure
Patients without Prior Events

Outcome	n/N Incident Rate[††] (95% CI)							
	Sub-cohort 1[†]		Sub-cohort 2[‡]					
			Sub-cohort 2a		Sub-cohort 2b		Sub-cohort 2c	
Gastrointestinal (GI)								
Gastrointestinal Disease	81/31139	10.93 (8.68, 13.59)	21/17525	6.04 (3.74, 9.24)	25/17899	6.87 (4.45, 10.14)	10/7901	6.84 (3.28, 12.57)
Gastrointestinal Medication	102/15354	30.04 (24.49, 36.47)	53/7870	37.10 (27.79, 48.53)	66/6725	53.74 (41.56, 68.37)	42/2446	103.78 (74.79, 140.28)
Renovascular								
Edema	133/28736	19.80 (16.57, 23.46)	71/16245	22.33 (17.44, 28.16)	67/16556	20.17 (15.63, 25.61)	29/7340	21.28 (14.25, 30.56)
Renal Impairment/Failure	19/33111	2.41 (1.45, 3.76)	13/18491	3.54 (1.89, 6.06)	7/18840	1.82 (0.73, 3.75)	2/8330	1.29 (0.16, 4.67)
Congestive Heart Failure								
Heart failure/Left ventricular dysfunction	37/32384	4.78 (3.37, 6.59)	14/18260	3.86 (2.11, 6.47)	9/18676	2.35 (1.08, 4.47)	2/8265	1.30 (0.16, 4.70)
Acute Vascular Events								
Cardiovascular System Event	99/29653	14.05 (11.42, 17.11)	37/16960	10.94 (7.70, 15.07)	37/17278	10.48 (7.38, 14.45)	23/7605	16.15 (10.23, 24.23)
Coronary Heart Disease	33/31788	4.35 (2.99, 6.11)	8/17949	2.23 (0.96, 4.40)	12/18358	3.19 (1.65, 5.57)	4/8101	2.65 (0.72, 6.78)
Acute Myocardial Infarction	30/32070	3.92 (2.64, 5.59)	7/18066	1.94 (0.78, 4.00)	12/18460	3.18 (1.64, 5.55)	4/8138	2.64 (0.72, 6.75)
Unstable angina pectoris	7/32805	0.90 (0.36, 1.84)	1/18413	0.27 (0.01, 1.52)	1/18783	0.26 (0.01, 1.45)	0/8313	0.00 (n/a, n/a)
Cerebrovascular Event	49/31924	6.44 (4.77, 8.52)	23/18032	6.43 (4.07, 9.64)	15/18333	4.01 (2.24, 6.61)	13/8129	8.57 (4.57, 14.66)
Intracerebral Haemorrhage	4/33209	0.50 (0.14, 1.29)	1/18586	0.27 (0.01, 1.51)	1/18923	0.26 (0.01, 1.44)	0/8366	0.00 (n/a, n/a)
Cerebral Infarction	7/33095	0.89 (0.36, 1.83)	5/18528	1.36 (0.44, 3.18)	4/18844	1.04 (0.28, 2.66)	2/8331	1.29 (0.16, 4.67)
Cerebrovascular Accident NOS[‡‡]	22/32778	2.81 (1.76, 4.26)	10/18396	2.74 (1.32, 5.04)	6/18731	1.57 (0.58, 3.42)	4/8286	2.59 (0.71, 6.64)
Transient Ischemic Attack	34/32388	4.41 (3.05, 6.16)	13/18219	3.59 (1.91, 6.15)	9/18563	2.37 (1.09, 4.51)	9/8235	5.88 (2.69, 11.16)
Arterial embolism / thrombosis	1/33215	0.13 (0.00, 0.70)	0/18595	0.00 (n/a, n/a)	0/18935	0.00 (n/a, n/a)	0/8374	0.00 (n/a, n/a)
Deep Venous Thrombosis	28/32343	3.64 (2.42, 5.25)	10/18172	2.78 (1.33, 5.12)	13/18510	3.45 (1.83, 5.89)	10/8142	6.62 (3.17, 12.17)
Pulmonary Embolism	12/32946	1.53 (0.79, 2.67)	3/18435	0.82 (0.17, 2.40)	9/18758	2.35 (1.07, 4.46)	0/8284	0.00 (n/a, n/a)
Sudden/unexplained death								
Sudden/unexplained death	2/33186	0.25 (0.03, 0.91)	1/18585	0.27 (0.01, 1.51)	2/18922	0.52 (0.06, 1.87)	0/8371	0.00 (n/a, n/a)
Acute Vascular event or sudden death								
Any acute vascular event or sudden/unexplained death	100/29596	14.23 (11.58, 17.30)	37/16945	10.94 (7.70, 15.08)	39/17252	11.07 (7.87, 15.13)	23/7598	16.16 (10.24, 24.25)

Outcome	n/N Incident Rate[††] (95% CI)							
	Sub-cohort 1[†]		Sub-cohort 2[‡]					
			Sub-cohort 2a		Sub-cohort 2b		Sub-cohort 2c	
Hypertension								
Diagnosis only	233/23638	43.22 (37.85, 49.14)	98/13324	37.90 (30.77, 46.19)	76/13333	28.47 (22.43, 35.63)	16/5968	14.45 (8.26, 23.47)
Diagnosis + medication	163/28534	24.40 (20.80, 28.45)	71/15999	22.72 (17.75, 28.66)	49/15908	15.24 (11.28, 20.15)	11/7075	8.34 (4.16, 14.93)
Cardiovascular medication								
Cardiovascular medication	35/14492	10.90 (7.59, 15.15)	26/8609	15.95 (10.42, 23.37)	19/7983	12.07 (7.27, 18.84)	11/3567	17.00 (8.49, 30.42)
Blood Pressure								
Blood Pressure Measurement	18/1478	58.69 (34.78, 92.76)	8/530	86.03 (37.14, 169.51)	6/384	98.34 (36.09, 214.05)	5/180	174.26 (56.58, 406.66)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods:
Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

[#] NOS=Not otherwise specified

[††] Per 1000 person year

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Table 15CT
Incident Rate of Clinical Outcomes
First Year Follow-up and First Course Exposure
Exposure Truncated when Other NSAIDs Prescription Written
Patients without Prior Events

Outcome	n/N Incident Rate[††] (95% CI)							
	Sub-cohort 1[†]		Sub-cohort 2[‡]					
			Sub-cohort 2a		Sub-cohort 2b		Sub-cohort 2c	
Gastrointestinal (GI)								
Gastrointestinal Disease	74/31139	10.81 (8.48, 13.57)	20/17525	6.14 (3.75, 9.48)	25/17899	7.33 (4.75, 10.83)	9/7901	6.57 (3.00, 12.47)
Gastrointestinal Medication	92/15354	28.85 (23.26, 35.39)	52/7870	38.46 (28.73, 50.44)	61/6725	52.62 (40.25, 67.59)	37/2446	96.12 (67.68, 132.49)
Renovascular								
Edema	125/28736	20.05 (16.69, 23.88)	66/16245	22.11 (17.10, 28.13)	63/16556	20.20 (15.52, 25.84)	25/7340	19.51 (12.63, 28.80)
Renal Impairment/Failure	17/33111	2.33 (1.35, 3.72)	12/18491	3.49 (1.80, 6.09)	6/18840	1.66 (0.61, 3.62)	2/8330	1.38 (0.17, 4.98)
Congestive Heart Failure								
Heart failure/Left ventricular dysfunction	35/32384	4.88 (3.40, 6.79)	13/18260	3.82 (2.03, 6.53)	9/18676	2.51 (1.15, 4.77)	2/8265	1.39 (0.17, 5.02)
Acute Vascular Events								
Cardiovascular System Event	91/29653	13.95 (11.23, 17.13)	34/16960	10.70 (7.41, 14.95)	37/17278	11.18 (7.87, 15.41)	22/7605	16.45 (10.31, 24.91)
Coronary Heart Disease	30/31788	4.27 (2.88, 6.10)	7/17949	2.08 (0.84, 4.29)	12/18358	3.40 (1.76, 5.95)	4/8101	2.82 (0.77, 7.23)
Acute Myocardial Infarction	27/32070	3.81 (2.51, 5.54)	6/18066	1.77 (0.65, 3.86)	12/18460	3.39 (1.75, 5.92)	4/8138	2.81 (0.77, 7.20)
Unstable angina pectoris	6/32805	0.83 (0.30, 1.80)	1/18413	0.29 (0.01, 1.62)	1/18783	0.28 (0.01, 1.55)	0/8313	0.00 (n/a, n/a)
Cerebrovascular Event	45/31924	6.39 (4.66, 8.56)	21/18032	6.25 (3.87, 9.56)	14/18333	3.99 (2.18, 6.70)	12/8129	8.44 (4.36, 14.75)
Intracerebral Haemorrhage	4/33209	0.55 (0.15, 1.40)	1/18586	0.29 (0.01, 1.61)	1/18923	0.28 (0.01, 1.54)	0/8366	0.00 (n/a, n/a)
Cerebral Infarction	5/33095	0.68 (0.22, 1.60)	3/18528	0.87 (0.18, 2.54)	4/18844	1.11 (0.30, 2.84)	2/8331	1.38 (0.17, 4.97)
Cerebrovascular Accident NOS[‡‡]	21/32778	2.90 (1.80, 4.44)	9/18396	2.63 (1.20, 5.00)	5/18731	1.40 (0.45, 3.26)	3/8286	2.08 (0.43, 6.06)
Transient Ischemic Attack	32/32388	4.48 (3.07, 6.33)	12/18219	3.53 (1.83, 6.17)	9/18563	2.53 (1.16, 4.81)	9/8235	6.27 (2.87, 11.90)
Arterial embolism / thrombosis	1/33215	0.14 (0.00, 0.76)	0/18595	0.00 (n/a, n/a)	0/18935	0.00 (n/a, n/a)	0/8374	0.00 (n/a, n/a)
Deep Venous Thrombosis	26/32343	3.65 (2.38, 5.35)	10/18172	2.96 (1.42, 5.45)	13/18510	3.68 (1.96, 6.29)	10/8142	7.05 (3.38, 12.96)
Pulmonary Embolism	11/32946	1.51 (0.76, 2.71)	3/18435	0.88 (0.18, 2.56)	9/18758	2.51 (1.15, 4.76)	0/8284	0.00 (n/a, n/a)
Sudden/unexplained death								
Sudden/unexplained death	2/33186	0.27 (0.03, 0.99)	1/18585	0.29 (0.01, 1.61)	2/18922	0.55 (0.07, 2.00)	0/8371	0.00 (n/a, n/a)

Outcome	n/N Incident Rate[††] (95% CI)							
	Sub-cohort 1[†]		Sub-cohort 2[‡]					
			Sub-cohort 2a		Sub-cohort 2b		Sub-cohort 2c	
Acute Vascular event or sudden death								
Any acute vascular event or sudden/unexplained death	92/29596	14.14 (11.40, 17.34)	34/16945	10.71 (7.42, 14.96)	39/17252	11.81 (8.40, 16.14)	22/7598	16.46 (10.32, 24.93)
Hypertension								
Diagnosis only	217/23638	43.35 (37.77, 49.51)	93/13324	38.20 (30.83, 46.79)	72/13333	28.62 (22.40, 36.05)	14/5968	13.37 (7.31, 22.44)
Diagnosis + medication	156/28534	25.19 (21.39, 29.47)	67/15999	22.84 (17.70, 29.00)	47/15908	15.57 (11.44, 20.70)	10/7075	8.04 (3.86, 14.79)
Cardiovascular medication								
Cardiovascular medication	33/14492	11.01 (7.58, 15.46)	25/8609	16.12 (10.43, 23.80)	17/7983	11.41 (6.65, 18.27)	11/3567	17.91 (8.94, 32.04)
Blood Pressure								
Blood Pressure Measurement	17/1478	58.74 (34.22, 94.05)	7/530	77.73 (31.25, 160.15)	6/384	102.37 (37.57, 222.82)	5/180	177.75 (57.72, 414.82)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods:
Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

[#] NOS=Not otherwise specified

[††] Per 1000 person year

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Table 16CT
Incident Rate of Clinical Outcomes
First Year Follow-up and First Course Exposure
Exposure Truncated when Other NSAIDs Prescription Written
Includes Patients with Prior Event

Outcome	n/N Incident Rate[††] (95% CI)							
	Sub-cohort 1[†]		Sub-cohort 2[‡]					
			Sub-cohort 2a		Sub-cohort 2b		Sub-cohort 2c	
Gastrointestinal (GI)								
Gastrointestinal Disease	85/33255	11.59 (9.26, 14.33)	23/18603	6.65 (4.22, 9.98)	27/18951	7.45 (4.91, 10.85)	11/8380	7.55 (3.77, 13.51)
Gastrointestinal Medication	326/33255	44.61 (39.90, 49.72)	248/18603	72.24 (63.53, 81.82)	332/18951	92.61 (82.91, 103.12)	266/8380	186.16 (164.46, 209.93)
Renovascular								
Edema	205/33255	28.11 (24.39, 32.23)	114/18603	33.17 (27.36, 39.85)	108/18951	29.98 (24.59, 36.19)	47/8380	32.36 (23.78, 43.03)
Renal Impairment/Failure	19/33255	2.59 (1.56, 4.04)	14/18603	4.05 (2.21, 6.79)	7/18951	1.93 (0.78, 3.98)	2/8380	1.37 (0.17, 4.96)
Congestive Heart Failure								
Heart failure/Left ventricular dysfunction	60/33255	8.18 (6.24, 10.53)	15/18603	4.34 (2.43, 7.16)	10/18951	2.76 (1.32, 5.08)	6/8380	4.12 (1.51, 8.96)
Acute Vascular Events								
Cardiovascular System Event	142/33255	19.40 (16.34, 22.87)	43/18603	12.46 (9.01, 16.78)	53/18951	14.66 (10.98, 19.18)	30/8380	20.62 (13.92, 29.44)
Coronary Heart Disease	45/33255	6.13 (4.47, 8.21)	11/18603	3.18 (1.59, 5.69)	13/18951	3.59 (1.91, 6.14)	5/8380	3.43 (1.11, 8.01)
Acute Myocardial Infarction	41/33255	5.59 (4.01, 7.58)	10/18603	2.89 (1.39, 5.32)	13/18951	3.59 (1.91, 6.14)	5/8380	3.43 (1.11, 8.01)
Unstable angina pectoris	8/33255	1.09 (0.47, 2.15)	2/18603	0.58 (0.07, 2.09)	1/18951	0.28 (0.01, 1.54)	0/8380	0.00 (n/a, n/a)
Cerebrovascular Event	66/33255	9.00 (6.96, 11.46)	23/18603	6.66 (4.22, 9.99)	19/18951	5.25 (3.16, 8.20)	14/8380	9.61 (5.25, 16.12)
Intracerebral Haemorrhage	4/33255	0.54 (0.15, 1.40)	1/18603	0.29 (0.01, 1.61)	1/18951	0.28 (0.01, 1.54)	0/8380	0.00 (n/a, n/a)
Cerebral Infarction	5/33255	0.68 (0.22, 1.59)	3/18603	0.87 (0.18, 2.54)	5/18951	1.38 (0.45, 3.22)	2/8380	1.37 (0.17, 4.96)
Cerebrovascular Accident NOS[‡‡]	28/33255	3.82 (2.54, 5.51)	9/18603	2.60 (1.19, 4.94)	7/18951	1.93 (0.78, 3.98)	3/8380	2.06 (0.42, 6.01)
Transient Ischemic Attack	40/33255	5.46 (3.90, 7.43)	14/18603	4.05 (2.21, 6.80)	10/18951	2.76 (1.32, 5.08)	10/8380	6.86 (3.29, 12.62)
Arterial embolism / thrombosis	1/33255	0.14 (0.00, 0.76)	0/18603	0.00 (n/a, n/a)	0/18951	0.00 (n/a, n/a)	0/8380	0.00 (n/a, n/a)
Deep Venous Thrombosis	32/33255	4.36 (2.98, 6.16)	12/18603	3.47 (1.79, 6.06)	14/18951	3.87 (2.11, 6.49)	12/8380	8.24 (4.26, 14.39)
Pulmonary Embolism	12/33255	1.63 (0.84, 2.86)	3/18603	0.87 (0.18, 2.53)	9/18951	2.48 (1.14, 4.72)	0/8380	0.00 (n/a, n/a)
Sudden/unexplained death								
Sudden/unexplained death	2/33255	0.27 (0.03, 0.98)	1/18603	0.29 (0.01, 1.61)	2/18951	0.55 (0.07, 1.99)	0/8380	0.00 (n/a, n/a)

Outcome	n/N Incident Rate[††] (95% CI)							
	Sub-cohort 1[†]		Sub-cohort 2[‡]					
			Sub-cohort 2a		Sub-cohort 2b		Sub-cohort 2c	
Acute Vascular event or sudden death								
Any acute vascular event or sudden/unexplained death	142/33255	19.40 (16.34, 22.87)	44/18603	12.74 (9.26, 17.11)	55/18951	15.21 (11.46, 19.80)	30/8380	20.62 (13.92, 29.44)
Hypertension								
Diagnosis only	376/33255	51.89 (46.78, 57.41)	123/18603	35.86 (29.80, 42.79)	103/18951	28.64 (23.38, 34.73)	21/8380	14.42 (8.93, 22.05)
Diagnosis + medication	214/33255	29.36 (25.56, 33.57)	75/18603	21.80 (17.15, 27.32)	65/18951	18.02 (13.91, 22.96)	13/8380	8.92 (4.75, 15.26)
Cardiovascular medication								
Cardiovascular medication	294/33255	40.21 (35.74, 45.08)	181/18603	52.60 (45.21, 60.84)	195/18951	54.07 (46.74, 62.21)	104/8380	71.81 (58.68, 87.02)
Blood Pressure								
Blood Pressure Measurement	354/33255	48.62 (43.69, 53.96)	214/18603	62.47 (54.38, 71.43)	299/18951	83.70 (74.48, 93.74)	268/8380	189.57 (167.55, 213.67)

[†] First etoricoxib prescription during the period 1 April 2002 through 17 February 2005

[‡] First etoricoxib prescription during the period 18 February 2005 through 30 Jun 2013. Divide the time period up into 3 periods:
Sub-cohort 2a: Feb 18, 2005-Dec 2007; Sub-cohort 2b: Jan 2008-Dec 2010; Sub-cohort 2c: Jan 2011-Jun 2013

[#] NOS=Not otherwise specified

[††] Per 1000 person year

10.6. Adverse events/adverse reactions

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.

11. Discussion

11.1. Key results

This report describes the seventh updated analysis and final results for a post-authorization commitment to the EMA to conduct a study to evaluate characteristics of patients prescribed etoricoxib, to describe patterns in the prescribing of etoricoxib by UK general practitioners (GPs), and to estimate the absolute incidence rate of adverse events (AEs) among new users of etoricoxib, using the UK CPRD. Since the CPRD does not preferentially select practices for participation, and the patients included in the database are felt to be representative of general practice patients in the UK, the results may be generalizable to the entire UK general practice patient population.

This update adds 3200 additional patients and additional follow-up time to the previous update by extending the cohort entry period an additional year to 30 June 2013 and the study follow-up period an additional year to 30 June 2014.

The results of this study indicate that over the study period 79,189 patients who met the study inclusion and exclusion criteria received an initial prescription for etoricoxib. Of these, 8,459 patients were "continuing users" defined as patients who received an initial prescription for etoricoxib before the 17 Feb 2005 COX-2 Urgent Safety Restriction and who subsequently received at least one additional etoricoxib prescription afterwards.

The rate of new etoricoxib prescribing increased from the time of market introduction for etoricoxib until October 2004, after which the number of new users fell sharply in the months leading up to the Urgent Safety Restriction. Following the Urgent Safety Restriction, the number of new users remained low and fairly constant during this study.

Of note, 43.0 and 50.3% of patients before and after the Urgent Safety Restriction, respectively, received only one etoricoxib prescription.

The characteristics of patients prescribed etoricoxib during the study period were as expected based on the labelled indications for use and the demographics of the study population. A sizable proportion of patients prescribed etoricoxib have a history of one or more risk factors for GI clinical events related to anti-inflammatory therapy (age, prior PUB, baseline history of prior NSAID, aspirin, corticosteroids, or oral anti-platelet drug use). In addition, about 36-43% of patients prescribed etoricoxib after the Urgent Safety Restriction have a baseline history of GI medication use (primarily H2 receptor antagonists or proton pump inhibitors). Thus, etoricoxib appears to be preferentially prescribed to patients with a history of or at risk for GI events, as has been described in previous studies. Such patients also tend to have a history of or be at risk for cardiovascular disease by virtue of the high prevalence of such conditions in the age range of the study population. Thus, it is not surprising that the baseline medical history data indicate that etoricoxib is prescribed to some patients with cardiovascular, cerebrovascular, and peripheral vascular disease and some patients with hypertension.

The mean (median) number of blood pressure measurements done during the baseline period (in the 12 months prior to receiving the initial etoricoxib prescription) was 1.8 (1) among patients first prescribed etoricoxib after the Urgent Safety Restriction and 2 (1) among continuing users. As was seen in the previous updated analysis, among patients prescribed etoricoxib after the Urgent Safety Restriction 11.7-14.3% have a baseline DBP ≥90 mm Hg, while 5.2-9.1% have a baseline SBP ≥160 mm Hg. However, this does not necessarily mean that the patient's BP was at those levels, or was not adequately controlled, when the first prescription for etoricoxib was written. As discussed in **Section 10.2. Results, Descriptive Data, Baseline Characteristics, Baseline Cardiovascular Risk Factors**, the median number of days between the latest baseline BP values in the patient's record and the initial prescription for etoricoxib was 215, 206, and 186 days for Sub-cohorts 1, 2 and 3, respectively. Therefore, the baseline blood pressure value for a given patient does not necessarily reflect that patient's blood pressure at the time etoricoxib was initially prescribed. Without an appropriate comparison group it is difficult to know whether these data are representative of the typical clinical care provided by GPs to patients treated with anti-inflammatory agents in the UK.

In other respects these results indicate the more recent prescribing of etoricoxib by GPs in the UK is generally consistent with the product labelling. In patients prescribed etoricoxib since the Urgent Safety Restriction the median initial doses prescribed and the duration of therapy are generally appropriate for each specific indication for use, when known.

In patients prescribed etoricoxib since the Urgent Safety Restriction, the incidences of clinical events of interest in this analysis are as expected given the characteristics of the patient population prescribed etoricoxib. Some of these estimates are imprecise due to sparse data for some events and for some sub-cohorts, especially for analyses of

subgroups. Among new users without prior events in Sub-cohort 2 (following the Urgent Safety Restriction) who were followed over a 1-year period, the incidences of potentially more serious clinical events, occurred uncommonly, with rates/1000py as follows: gastrointestinal events (perforations, ulcers and bleeds) 6.5, renal impairment or failure 2.4, congestive heart failure 2.8, coronary heart disease events 2.7, strokes 0.2-2.2, pulmonary embolism 1.3. Acute vascular (cardiac, cerebrovascular, peripheral vascular) events of any type occurred at a rate of 11.9/1000py (1.1%/yr). See below for discussion regarding the rates of MI and strokes compared with UK National statistics and etoricoxib clinical trials. The incidence of new onset hypertension (defined as the presence of a diagnosis + antihypertensive prescription in the medical record) occurred at 17.1/1000py, or about 1.7% per year. As expected, most clinical events were more commonly observed in older patients. There is not sufficient data to draw clear conclusions about dose-response relationships between etoricoxib exposure and the more important clinical events.

The additional analyses performed for the final report did not demonstrate that OA and RA patients taking higher than labelled doses had rates of health outcomes of interest that were consistently higher than patients taking standard doses. In addition, the analysis looking at patterns of clinical events over time (from Sub-cohort 1 through 3 periods within Sub-cohort 2) showed no consistent pattern of increased health outcomes of interest over time.

The incidence rates of MI, stroke and heart failure outcomes in this study can be compared with UK national statistics provided by the British Heart Foundation (BHF) [Ref. 5.4: 048ML6]. However, such comparisons may not be completely accurate for a number of reasons, including different populations from which the data are collected (general population vs. patients with specific medical conditions / drug use), different distributions of age and other important covariates, different surveillance methods, different dose distributions, different outcome definitions, etc.). Data from the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Program of studies (three studies in patients with OA and RA) [Ref. 5.4: 03Q663] are also used for comparison purposes; although this comparison also may not be completely accurate for some of the same reasons.

In the UK in 2012-13, the incidence of MI among men and women of all ages was 355 and 203/100,000, respectively. [Ref. 5.4: 048ML6] (Table 2.1). In the current study patients prescribed etoricoxib after the Urgent Safety Restriction (mean (sd) age of about 58 (15.9) years, 57.0% female), the MI incidence in those without prior MI (**Table 14**) is estimated to be 271/100,000 (95% CI: 174, 403) and 340/100,000 (95% CI: 227, 488) when patients with prior events are included (**Table 16**). Considering the age and gender distribution of the current study population and the confidence intervals around the estimates, these rates are generally in the same range as those estimated for the UK by the British Heart Foundation (BHF). In the MEDAL Program [Ref. 5.4: 03Q663], the incidence of fatal and nonfatal MI (111 events in 25,836 py) was about 430/100,000 py,

which is numerically higher than the rate of MI that was observed in Sub-cohort 2 in this study.

In the UK in 2012-13, the incidence of stroke among men and women of all ages was 371 and 372/100,000, respectively. [Ref. 5.4: 048ML6] (Table 2.1). In the current study, with a mean (sd) age of about 58 (15.9) years in those patients prescribed etoricoxib after the Urgent Safety Restriction (57.0% female), the cerebral infarction incidence in those without a prior stroke (**Table 14**) is estimated to be 121/100,000 (95% CI: 61, 217) and 117/100,000 (95% CI: 56, 215) when patients with prior events are included (**Table 16**). Also in the current study, the incidence of strokes not specified as ischemic or haemorrhagic in those without a prior history of stroke (**Table 14**) is estimated to be 222/100,000 (95% CI: 136, 343) and 222/100,000 (95% CI: 134, 347) when patients with prior events are included (**Table 16**). Considering the age and gender distribution of the current study population and the confidence intervals around the estimates, these rates are generally in the same range as those estimated for the UK by the BHF. In MEDAL Program [Ref. 5.4: 03Q663] the incidence of fatal and nonfatal ischemic strokes (59 events in 25,836 py) was about 228/100,000 py, which is numerically higher than the rate of cerebral infarction and similar to the rate of cerebrovascular accident not specified as ischemic or haemorrhagic in Sub-cohort 2 in this study.

The incidence rates of heart failure in the UK in 2012-13 among men was 256/100,000 person-years, while that among women was 226/100,000 person-years [Ref. 5.4: 048ML6] (Table 2.1). In the current study, in those patients prescribed etoricoxib after the Urgent Safety Restriction (mean [sd] age of about 58 [15.9] years; 57.0% female), the heart failure incidence in those without prior heart failure (**Table 14**) is estimated to be 278/100,000 (95% CI: 180, 410): and 363/100,000 (95% CI: 247, 515) when patients with prior events are included (**Table 16**). These rates are somewhat higher than those estimated for the UK as a whole by the BHF. In the MEDAL Program, AE reports of heart failure were adjudicated by an external, blinded committee. The incidence of heart failure reports sent for adjudication, as well as those confirmed as heart failure by the committee were analysed overall (for all studies and doses of etoricoxib combined). Among 17,412 patients treated with etoricoxib the rate (95% CI) of reports (n=51) sent for adjudication was 350/100,000 (260, 460) and the rate (95% CI) of reports (n=40) confirmed as heart failure was 280/100,000 (200, 380) [Ref. 5.4: 03Q527]. The rate of reports sent for adjudication is likely a more appropriate comparison rate for the present study since the diagnoses in the CPRD database are not similarly adjudicated by experts. The rate of heart failure among patients without a prior diagnosis in the current study is comparable with the above overall rate of heart failure AEs sent for adjudication in the MEDAL program studies, by virtue of the overlap in the 95% CIs for the two estimates. It is important to note that 61% of patients (n=10,643) in the MEDAL program were taking 90 mg of etoricoxib daily [Ref. 5.4: 03Q663] , and the rate of confirmed heart failure with etoricoxib 90 mg in a pooled analysis of the MEDAL program studies was 423/100,000 (calculated from Figure 2 in [Ref. 5.4: 03RS96]. In the current study, 28% of patients in Sub-cohort 2 were initially prescribed 90 mg of etoricoxib. In the current study, the sub-cohort dose-specific incidence rates/100,000 (95% CI) of heart failure

without prior events with use of etoricoxib 30, 60, 90 and 120 mg are 0, 307 (163,525), 282 (122,555), and 433 (118,1110), respectively. The rates for 60, 90 and 120 are based on 13 events in 19,527 patients, 8 events in 12,862 patients, and 4 events in 8437 patients, respectively which are slightly lower than last year. Although the point estimate for heart failure incidence with etoricoxib 120 mg is higher than the lower doses, interpretation of a dose response trend is not possible due to the imprecision at the different dose levels, as reflected in the widely overlapping dose-specific confidence intervals for the rates and the non-monotonically increasing rates.

It has previously been demonstrated that use of NSAIDs or COX-2 inhibitors is associated with heart failure [Ref. 5.4: 03RS5D]. The ARCOXIA EU SPC 20 Sep 2008 section 4.3 (Contra-indications) includes patients with heart failure (NYHA II-IV), and section 4.4 (Special warnings and precautions for use) includes heart failure in the item on "Fluid retention, oedema and hypertension". The SPC also states "In the individual MEDAL Program studies, for etoricoxib (60 mg or 90 mg), the absolute incidence of discontinuation in any treatment group was up to … 1.1% for congestive heart failure, with higher rates of discontinuation observed with etoricoxib 90 mg than etoricoxib 60 mg."

Overall, the results of this study do not change the previously established favourable benefit-risk profile for etoricoxib.

11.2. Limitations

This study has potential limitations that should be recognized:

1) The data from this study are from GPs. In the UK, most consultations (e.g. doctor visit, prescription, specialist referral) occur in primary care. However, the GPs will not typically capture health services provided by direct access to some health care providers including the emergency room.
2) Drug exposure to etoricoxib was based on prescriptions written (rather than on pharmacy dispensing data or on actual patient observation); this is expected to over-estimate actual use of etoricoxib in the study population because some patients never fill their prescriptions and among those who do fill their prescriptions some do not consume the entire quantity of tablets dispensed to them. In addition, exposure during admissions to hospital cannot be assessed. In light of the fact that this study will measure GP prescribing and not actual drug use by patients, any inferences about drug use 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 the drugs under study as directed on consecutive days after the date that each prescription was issued; 3) patients consumed the entire quantity of drug supplied in each prescription, and 4) the patient was not hospitalized during a period of exposure. It is unlikely that all of these assumptions hold, and the effect on the results of the study are unknown.

3) Prescriptions issued outside of a patient's primary care practice by hospital-based specialists also are not captured in the CPRD; however, we anticipate this source of etoricoxib would be small relative to that from GPs.

4) Sample selection bias is possible to the extent that the prescribing behaviour of the GPs in our study sample is not representative of the prescribing behaviour of all GPs in the UK.

5) 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. Incomplete coding of musculoskeletal disease (e.g., diagnoses from specialists that are not recorded in the primary care records) may account for the large percentage of "unknown (none of the above)" indications for etoricoxib treatment in this study.

6) 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.

7) 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.

8) The clinical outcomes under study are based on GP recorded diagnoses based on clinical care standards. Changes in clinical outcome definitions over time should be considered in light of the study findings. It is expected that there will be some degree of misclassification of clinical outcomes due to misdiagnoses, or to the fact that some codes are entered as provisional diagnoses for hospital referrals. There may be a greater proportion of erroneous diagnoses for some outcomes (TIA, hypertension) compared with others (MI, acute renal failure).

The net effect of these potential limitations on the study results is unknown.

11.3. Interpretation

This updated analysis of 79,189 patients prescribed etoricoxib during the study period suggests that etoricoxib is, in general, appropriately prescribed to patients with chronic indications for etoricoxib therapy. A large proportion of patients prescribed etoricoxib do not have a recorded explicit diagnosis for a labelled indication for etoricoxib in the medical record. The addendum to this report (Annex 3, Part B) describes the clinical characteristics of this group of patients. Note that the fact that no specific terms were recorded for one of the labelled indications does not necessarily mean that patients were treated 'off label'. For example, many GP's may record a less-specific diagnosis such as "knee pain", which could well be OA or RA but not recorded as such. Such less-specific diagnoses are often consistent with one or more of the diagnoses for a labelled indication, and therefore, it is difficult to estimate the proportion of patients treated without one of

the labelled indications. Moreover, patients may be diagnosed by specialists in secondary care but prescribed etoricoxib by their GPs in primary care. Thus, in the CPRD, we see a prescription for etoricoxib recorded by GPs, but because records from secondary care are not included in the CPRD, we do not see diagnoses (possibly for a labelled indication) which may be associated with an etoricoxib prescription recorded by specialists. The baseline characteristics of the population are as expected given the indications for therapy, including the common occurrence of risk factors for GI and CV clinical events. Some patients prescribed etoricoxib have baseline BP measures ≥160 mm Hg systolic or ≥90 mm Hg diastolic; however, those measures are frequently done much earlier in time than the date that etoricoxib was initially prescribed. The doses and duration of initial etoricoxib prescriptions / courses of therapy are generally consistent with labelling and appropriate given the benefit-risk profile of the drug. Prescribed dosages do not appear to be increasing over time. The incidences of AEs of special interest with use of etoricoxib are as expected for the NSAID class. Among new users without prior events who were first prescribed etoricoxib after the Urgent Safety Restriction and who were followed over a 1-year period, the incidences of potentially more serious clinical events occurred uncommonly and generally at lower rates than the cohort first prescribed etoricoxib before the Urgent Safety Restriction. Event rates for the health outcomes of interest are not consistently higher for OA and RA patients taking higher than labelled dosages, and rates of the AE's of special interest do not appear to be increasing over time. Overall, the results of this analysis suggest, given the characteristics of the patient population, the safety profile of etoricoxib in general clinical practice is consistent with the safety profile of the product as previously demonstrated during clinical development and through post-marketing pharmacovigilance.

11.4. Generalisability

The CPRD includes 5.72 million currently active patients with research quality data and 13.5 million persons with research usable data from 683 practices, with research quality data collected since 1987. The database (8.5% of the UK population) is generally representative of the UK general population; thus, results are generalizable to the UK general population and likely to many other EU member states with similar populations.

12. Other information

This study is funded entirely by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA

13. Conclusion

Overall, the results of this analysis suggest, given the characteristics of the patient population, the safety profile of etoricoxib in general clinical practice is consistent with the safety profile of the product as previously demonstrated during clinical development and through post-marketing pharmacovigilance and as reflected in the SmPC. Overall,

the results of this study do not change the previously established favourable risk profile for etoricoxib.

14. References

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