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Clinical Practice Research Datalink

Amendment to Protocol Number: 06_008

Etoricoxib Prescribing Patterns and Adverse Events of Interest during Etoricoxib Treatment in UK Primary Care: a Descriptive Analysis of "Off-label" Use

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1. BACKGROUND

This amendment to the protocol titled "Etoricoxib Prescribing Patterns and Adverse Events of Interest during Etoricoxib Treatment in UK Primary Care: an Updated Analysis" (the primary study) describes additional analyses of the subset of the study population prescribed etoricoxib "off-label". The analyses described will be performed as part of the scheduled annual updates to the original analysis, beginning in 2013. The results of the proposed analyses will be included in the updated study report for 2013, and annually thereafter.

2. PURPOSE

This amendment describes analyses of patients in the primary study population who are treated with etoricoxib "off-label". This includes pediatric patients less than 16 years of age, and adult patients in the CPRD GOLD (formerly GPRD) who do not have one of the labeled indications for treatment with etoricoxib pre-specified for the primary study (i.e., OA, RA, AS, gout, or arthritis not specified).

These patients will be studied to better understand the baseline medical histories of these patients and how they are treated with etoricoxib by general practitioners in the UK.

3. SPECIFIC OBJECTIVES

The specific objectives of this amendment are to describe:

a. Baseline characteristics and treatment with etoricoxib in pediatric patients (aged <16 years) in the primary study population.

b. Baseline characteristics and treatment with etoricoxib in adult patients (aged >=16 years) who do not have a labeled indication for treatment with etoricoxib. For the adult population, the three sub-cohorts defined in the primary protocol will be examined as described in the purpose section of the primary protocol.

4. STUDY POPULATION

As described in **Section 4** of the protocol of the primary study, the study population will include all patients in the MHRA's CPRD GOLD who have at least one electronic outpatient prescription record for etoricoxib issued during the period (1 April 2002 to 31 December 2011) at the date of query execution against the data warehouse. Section 4 of the protocol of the primary study outlines the exclusion criteria of the study population.

The pediatric patient population will include all patients <16 years of age in the primary study population. The adult "off-label" population will include all adult patients (age >=16 years) in the original study population who did not have one of the labeled indications for treatment with etoricoxib pre-specified for the primary study (i.e., OA, RA, AS, gout, or arthritis not specified).

5. STUDY DESIGN, METHODS, AND ANALYSES

This is a retrospective cohort study of all patients in the CPRD GOLD who have at least one electronic outpatient prescription record for etoricoxib issued during the period 1 April 2002 to 30June2013 (with each annual update to the analysis an additional calendar year will be added to this time period to accrue additional patients newly prescribed etoricoxib since the prior year). The study design, methods, and analyses for the pediatric and adult "off-label" patient populations are described below:

Pediatric patients (<16 years old)

All diagnoses during the period +/-7 days of the date of the first etoricoxib prescription will be listed and the indication for etoricoxib will be presumed based on clinical review. Demographic, dosing information, duration of therapy, and number of prescriptions received will be described and presented as shown in Table shells 1 and 2.

Adult "off-label" patients (>=16 years old)

Patient characteristics (Table shell 3), baseline characteristics of interest (Table shells 4-6), and non-clinical outcomes of interest (Table shells 7-14) will be analyzed and described as outlined in the study design and study analysis sections of the primary protocol. The distribution of diagnosis codes listed on the date of etoricoxib prescription will be extracted and clinically reviewed to determine whether sub-groups of adult "off-label" patients can be defined according to higher level diagnosis codes and their clinical descriptions (e.g., dysmenorrhea, musculoskeletal injury, post-operative pain, among others). If this is feasible the analyses described above will be performed stratified by such groupings and examined for clinically meaningful differences.

The above analyses will be included with each annual update to the primary study analysis starting with the 2013 annual update.

6. STUDY PERIOD

The study period for the analysis will commence on 1 April 2001 and will end on 30 June 2014, as for the primary protocol. With each annual update to the analysis an additional calendar year will be added to the study period.

7. POTENTIAL LIMITATIONS

This analysis will have potential limitations as outlined in Section 14 of the protocol of the primary study. In particular, there is no direct linkage between a prescription for etoricoxib and a diagnosis in the medical record of a patient in the CPRD GOLD. Therefore, characterization of diagnoses for which etoricoxib is prescribed in the pediatric patients and adult "off-label" patient populations described in this amendment will rely on clinical judgment on the part of the investigators which are not able to be verified with the current study design and methods. In addition, small numbers, particularly for the pediatric patient population, will limit the ability to make conclusions on the findings for this descriptive analysis of "off-label" use.