Impact of EU label changes for hydroxyzine products: post-referral prescribing trends

Study Protocol

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Contents

1 BACKGROUND

Hydroxyzine is a first-generation antihistamine with indications in Europe for the management of anxiety disorders, skin conditions (such as pruritus, dermatitis or urticaria), for preoperative sedation and sleep disorders. Within Europe, formulations of hydroxyzine containing medicinal products are available as film-coated tablets, oral syrup, a gel or a solution for injection.

In February 2015, an EMA referral procedure was raised to the Pharmacovigilance Risk Assessment Committee (PRAC) to examine the potential risk of QT interval prolongation and cardiac arrhythmia of hydroxyzine products based upon evidence from clinical and post-marketing data.[1] [2] [3] This effect is considered due to an inhibitory effect on cardiac channels including hERG. [4]

The referral procedure concluded that although hydroxyzine containing products are effective treatments for their approved indications, hydroxyzine products are associated with an elevated risk of QT prolongation and cardiac arrhythmia particularly in the at-risk population as consisting of patients with risk factors for QT interval prolongation.

The referral procedure concluded (on 27 March 2015) that in order for the benefit-risk balance of hydroxyzine containing medicinal products to remain favourable, contraindications, warnings, dose restrictions and changes to the product information, including direct healthcare professional communication (DHPC) were required to be implemented across the EU.

The EMA implemented risk minimisation measures relating to the use of hydroxyzine in 2015. The main elements of this were as follows:

- Hydroxyzine be restricted to a maximum daily dose of 100 mg per day in adults with corresponding changes in the paediatric and elderly populations, based on pharmacokinetic data and with the treatment duration as short as possible.
- Hydroxyzine be contraindicated in patients with a known acquired or congenital QT interval prolongation and in patients with a known risk factor to QT interval prolongation including a known cardiovascular disease, significant electrolytes imbalance (hypokalaemia, hypomagnesaemia), family history of sudden cardiac death, significant bradycardia, concomitant use with other drugs known to prolong the QT interval and/or induce Torsades de Pointes.
- Changes made to the Summary of Product Characteristics (SmPC) and package leaflet, including a revision of the posology and a warning that use in the elderly is not recommended due to the anticholinergic effects.

As part of the PRAC strategy for measuring the impact of pharmacovigilance, the aim of this study is to measure the effectiveness of regulatory actions taken for hydroxyzine containing medicinal products following the 2015 referral procedure, with the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation date of 12 February 2015 and the Committee for Medicinal Products for Human Use opinion / Coordination Group for Mutual Recognition and Decentralised Procedures – Human position date of 25 March 2015 (the date the recommendation became legally binding across the EU).

2 AIM

To evaluate the impact of the risk minimisation measures implemented in 2015 to manage the cardiovascular risks of systemic hydroxyzine containing medicinal products authorised in the European Union (EU) in clinical practice.

3 OBJECTIVES

Our objective is to measure the impact of the risk minimisation measures, which drew attention to new contraindications, warnings, and other changes to the product information. We will analyse trends in prescribing patterns from a minimum of six years before the intervention (the maximum available data in Scotland) for as long as each database allows. We will provide these trends by age and gender, and where possible by indication for hydroxyzine.

There are three broad objectives:

3.1 OBJECTIVE 1: TO DETERMINE PRESCRIPTION PATTERNS OF HYDROXYZINE CONTAINING PRODUCTS

To determine drug utilisation and prescription patterns of hydroxyzine containing medicinal products (ATC (Anatomical Therapeutic Chemical) codes: N05BB01, N05BB51), and to investigate whether significant changes in prescribing patterns have occurred in clinical practice following the 2015 referral. This objective will particularly focus upon measuring:

- Prescription and utilization of hydroxyzine containing medicinal products in initiators, by indication, by age, by gender and by country;
- Discontinuation of hydroxyzine containing medicinal products, and changes in dose and duration of therapy, including prescription of a maximum daily dose of 100 mg (in adults) and for the shortest possible duration;
- Time trends in prescribing over a minimum of at least six years before the regulatory intervention (i.e. implementation of dose restriction, new contraindications, warnings, and other changes to the product information, and the dissemination of the DHPC) and ideally including data up to 2017.

For CPRD/PHARMO databases, diagnoses codes to identify clinical indications will be captured at the primary care level whilst for Scottish/Danish databases these codes will be captured within secondary care data consisting of outpatient (Denmark only) and inpatient diagnoses data (Scotland/Denmark). Please see Appendix 1 for list of codes to define clinical indications within each database.

The primary analysis will calculate prescription patterns for overall hydroxyzine prescribing (based upon any type of hydroxyzine-containing product) before and after the regulatory intervention as:

i. initiation rates
ii. prescribing rates by patients
iii. prescribing rates by prescriptions
iv. discontinuation rates
v. daily dose
vi. duration

This will be done for all patients exposed and then by indication, by age and by gender. Secondary analysis will calculate prescription patterns for each dosage form (tablets or solution) for any indication and then by indication, age and gender.

3.2 OBJECTIVE 2: TO DETERMINE PRESCRIBERS COMPLIANCE WITH RECOMMENDATIONS

To determine prescribers' compliance with recommendations included in sections 4.2, 4.3 and 4.4 of the Summary of Product Characteristics for hydroxyzine containing medicinal products, by country, by

indication (i.e. anxiety disorders, skin conditions, preoperative sedation, sleep disorders), by age and by gender.

We will assess compliance with recommendations included in sections 4.2, 4.3 and 4.4 of the Summary of Product Characteristics for hydroxyzine containing medicinal products by calculating prescription patterns in overall hydroxyzine prescribing rates and hydroxyzine initiation rates among patients with a history of the following contraindications:

i. Established cardiovascular disease
ii. Patients with a recent history of significant electrolytes imbalance (hypokalaemia, hypomagnesaemia)
iii. Family history of sudden cardiac death (in databases where this is recorded)
iv. Recent symptomatic bradycardia (recent code for bradycardia or pulse rate <60 BPM)
v. Concomitant use with drugs known to prolong the QT interval (see appendix)
vi. Concomitant use with drugs known to induce Torsade de Pointes (see appendix)

For overall hydroxyzine prescribing this will first be done for all patients exposed and then by indication, age and gender.

3.3 OBJECTIVE 3: TO DETERMINE PRESCRIPTION PATTERNS OF ALTERNATIVE MEDICINES PRESCRIBED IN PATIENTS WHERE HYDROXYZINE HAS PREVIOUSLY BEEN PRESCRIBED

To determine drug utilisation and prescription patterns over time for alternative medicines that have been prescribed to patients where hydroxyzine has previously been prescribed or discontinued, by country, by indication (i.e. anxiety disorders, skin conditions, sleep disorders), by age and by gender.

Among patients who discontinue hydroxyzine therapy (and where the indication is known) we shall calculate prescription patterns in the proportion who subsequently initiate treatment with alternative therapies for:

i. anxiety disorders
ii. skin conditions
iii. sleep disorders

Please see Appendix for list of codes used to identify these drugs. Following initial scoping of the data sources for this study, we do not propose including the preoperative sedation indication, as hydroxyzine is not licenced for this indication in the counties involved with this study and we do not have access to the required secondary care prescribing records. Secondary care settings have traditionally been very poor at capturing patient level prescribing. Such datasets are in development in Scotland and other parts of the UK, but are not yet sufficiently validated or well established for studies of this nature.

4 DATA SOURCE SUMMARIES

Four validated population data sources[4-9] will be used.

4.1 SCOTLAND, UK

The Prescribing Information System (PIS) records all medicines dispensed from pharmacies in Scotland (population estimated 5.3 million in June 2014) and these can be record-linked using the person-unique Community Health Index (CHI) number to demographic data (e.g. age, sex, social deprivation, dates registered with family doctor), Scottish Morbidity Records (e.g. SMR01 – in-patient hospitalisations) and

National Records of Scotland (NRS) death registrations for the entire population (International Classification of Diseases (ICD)-9/ICD-10 coded). Prescription data is available from 2009. [5]

4.2 DENMARK

The Danish Register of Medicinal Products records all out-of-hospital prescriptions (full population coverage of 5.6 million individuals). A unique 10-digit personal identifier, the Centrale Person register (CPR) number,[5] readily allows linkage of drug exposures to outcomes in the form of ICD-10 diagnoses registered in connection with inpatient and outpatient hospital contacts.[6] [7]Death data is available from the Civil Registration System. Prescription data is available from 1995.[8]

4.3 CLINICAL PRACTICE RESEARCH DATALINK (CPRD), UK

CPRD contains data originating from the computer systems of General Practitioners (GPs) across the United Kingdom with an estimated 6 million population. The data has been collected since 1987, it covers about 7% of the UK population and is broadly generalisable to the whole UK population. [9] For this study, data will be taken from all non-Scottish "up to standard" practices. Data on diagnostic coding and prescribing come from the GP system and are recorded as Read, Gemscript and BNF codes.

4.4 PHARMO DATABASE NETWORK, NETHERLANDS

The PHARMO Database Network is a population-based network of electronic healthcare databases and combines data from different primary and secondary healthcare settings in the Netherlands. To address the objectives of the present study the Out-patient Pharmacy and the GP Database will be used. The Out-patient Pharmacy Database of the PHARMO Database Network comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy (population 4.2 million in 2016). Dispensing data is available from 1998 and ongoing. These data can be linked on a patient-level using probabilistic linkage to other databases. Data on indication and contraindications are obtained from the GP Database for a population of approximately 1 million. This database comprises data from electronic patient records registered by GPs. Dispensing data is recorded as ATC and diagnoses as ICPC (International Classification of Primary Care) codes or entered as free text. For this study, only the ICPC coded data will be used. ICPC codes can be mapped to ICD codes. [10]

5 STUDY METHODS

Population-based longitudinal studies will be conducted across these four databases using this common protocol that will be registered in the EU PAS (post-authorisation studies) Register.

5.1 OVERVIEW

Population-based longitudinal studies will be conducted using the four databases. A common protocol will be used to extract data from each data source and code lists will be agreed *a priori* by members of the consortium. A protocol will be submitted to the Agency prior to commencing and the final approved study protocol will be registered in the EU PAS (post-authorisation studies) Register.

Individual patient data sets will be assembled in each country and will not be transferred out of the country. The list of variables included in the study are defined in this document. Some of these variables are not available in every country. Analyses will be conducted separately for each country and when a variable (e.g. smoking status) is not available in a country the relevant sub-tables will not be produced. No imputation of missing values will be done, and if a variable is unknown for an individual subject it will be classified as such. The different database structures and coding systems used by each country mean that

different logic will be used to calculate each of the variables listed here. These will be reviewed for consistency between countries. To further improve consistency a high-level data extraction plan will be used, for each country to adhere to. An aggregate data set will be prepared in each country and forwarded to the lead institution providing the minimum count per time point contains greater than or equal to five patients per cell to meet with local data protection and disclosure control requirements. A central study statistician based at the lead institution will analysis the combined data, which will consist of a full cross classification of the data by all the stratification variables, and by time point.

5.2 STUDY PERIOD

The study period will start on 01/01/2009 for all data sources. The end of data collection will be 31/12/2017 or later where data are available.

5.3 STUDY POPULATION

The study population will consist of all patients registered within each data source at any time during the study period. The first follow-up date for a patient will be defined as the date of registration with the general practice (CPRD and PHARMO), or date of first recorded prescription or any secondary care diagnosis (Denmark and Scotland). A patient's index date will be the latest of the study period start date (01/01/2009 for Scotland), the (approximate) date of birth, or their first database follow up date plus 1 year (to allow sufficient time for data on baseline covariates to be collected – neonates will be followed up from birth without this 1-year restriction). A patient's last follow up date will be the first occurrence of the following: death (all databases); end of study period (varies between countries); end of registration (end of registration will not significantly affect data from Denmark and Scotland because they use national data that captures patients moving within the health system). A patient is included for analysis in a time period if the first and last day both lie between the patient's index date and their last follow up date, so the analyses will only include patients who are observable for the entire time period (i.e. incomplete quarters will be excluded resulting in the loss, on average, of the last 46 days of each patient's observation period; if retained, these partial quarters would introduce bias in some measures.).

5.4 EXPOSURE DEFINITIONS

For objective 1, the principal exposure to hydroxyzine containing medicinal products (ATC codes: N05BB01, N05BB51) will be measured for all formulations (tablets, oral syrup, a gel or a solution for injection).

For objective 2, the exposure definitions used for objective 1 will be applied to each of the contraindicated and high-risk groups outlined in section 3.2.

For objective 3, the principal exposure will be 1) other prescribed antihistamine-containing medicinal products, 2) benzodiazepine-containing medicinal products, and 3) other sedative containing medicinal products. Drug lists for each will be independently developed for each data source, in agreement with the Agency.

5.5 OUTCOME VARIABLES

The primary outcomes are changes in prescribing patterns of hydroxyzine and related medicines. This will be measured for all patients, for initiators and for people discontinuing hydroxyzine containing medicinal products. Initiators (new users) will be defined using time periods without any hydroxyzine exposure such as none in the previous 3 months.

This will be done for all products and by different formulations (tablets, oral syrup, gel and solution for injection).

For each of the objectives listed above we will analyse a series of proportions evaluated in each time point over the study period. The denominators are all patient counts. The numerators are either patient counts or numbers of prescriptions.

5.6 STRATIFICATION VARIABLES

Drug utilisation and prescribing trends will be plotted for hydroxyzine and related medicines stratified by the following variables:

5.6.1 Age and gender

These data will be taken from basic demographic data in each database. Age will be classified as 0-17, 18-29, 30-39, 40-49, 50-59, 60-69, 70-79 or 80+.

5.6.2 Indications for hydroxyzine

The indication for hydroxyzine is typically not directly linked to the dispensing record. Diagnostic codes for anxiety, skin problems and sleep disorders recorded predominantly in primary care (CPRD & PHARMO) and use of disease specific medicines (e.g. selective serotonin reuptake inhibitors, benzodiazepines, topical products for the treatment of skin disorders) will be used as a proxy for diagnosis. Hospitalised diagnoses (from inpatient and outpatient records as applicable) will also be used in Scotland and Denmark to identify indications. The classification will be based on any record dated before the end of the time point.

5.6.3 Contraindicated groups

Patients with a history of known QT interval prolongation, cardiovascular disease (congestive heart failure, ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease), symptomatic bradycardia, significant electrolyte imbalance will be identified within each of the databases through Read codes (CPRD), ICPC codes (PHARMO) and ICD codes (Denmark and Scotland). Within each data source, a cohort of patients will be created for each of the contraindicated groups in order to meet objective 2 of the tender specification.

5.6.4 Concomitant use with other drugs known to prolong the QT interval

Patients with concomitant (supplied with a sufficient quantity to overlap with use of hydroxyzine) use of other drugs known to prolong the QT interval and/or induce Torsades de Pointes will be identified by prescriptions in each database. Lists of such drugs will be developed for each data source, in agreement with the Agency.

5.7 OBJECTIVE 1: DEFINITIONS TO DETERMINE PRESCRIPTION PATTERNS OF HYDROXYZINE CONTAINING PRODUCTS

5.7.1 Objective 1.1: Hydroxyzine initiation rates

Hydroxyzine initiation is defined as a prescription for hydroxyzine with no exposure to hydroxyzine in the preceding 92 days. Sensitivity analyses will be carried out with a non-exposure period of 180 days instead of 92 days. The denominator is the number of non-users on the first day of the time period defined as no exposure to hydroxyzine in the previous 92 days. The numerator is the number of these patients initiating hydroxyzine in the time period. Patient will only be counted in the numerator if they are also counted in the denominator.

5.7.2 Objective 1.2: Overall hydroxyzine prescribing rates by patients

For overall hydroxyzine prescribing rates, the denominator is defined as the number of observable patients on the first day of the time period (both hydroxyzine users and non-users). The numerator is defined as the number of these patients with any prescription for hydroxyzine in the time period. The exception will be for Denmark where the denominator will be the number of patients present in the cohort on 1st January each year. The calculation is limited to those patients who complete the time period.

5.7.3 Objective 1.3: Overall hydroxyzine prescribing rates by prescriptions

Hydroxyzine prescribing rates will also be assessed at the prescription level among hydroxyzine users. The denominator is the number of patients prescribed hydroxyzine in the cohort in the time period. The numerator is the number of prescriptions they received.

5.7.4 Objective 1.4: Hydroxyzine discontinuation rates

Discontinuation is defined as the number of patients with a prescription for hydroxyzine with no exposure to hydroxyzine in the 92 days following the end of the date of that hydroxyzine prescription. The denominator is the number of patients prescribed hydroxyzine in the time period. The numerator is the number of these patients discontinuing. Sensitivity analyses will be carried out with a 180 day time interval instead of 92 days. Death will not be treated as a special case. Any end of observation period dates will result in an incomplete final quarter and accordingly be dropped.

5.7.5 Objective 1.5: Prescribed dose of hydroxyzine

This requires the calculation of an average total daily dose of hydroxyzine prescribed for each hydroxyzine-exposed patient during the time period. Average daily dose during a continuous treatment episode will be calculated as (strength x quantity summed over all prescriptions in the episode) / (length of episode including unexposed days). This will allow the dose to be calculated from strength and quantity and will be available for all data sources [not Denmark though?]. Further details will be provided in the Data Extraction Plan.

5.7.6 Objective 1.6: Duration of hydroxyzine

Given that hydroxyzine is used to treat frequently transient symptomatic conditions, it is anticipated that most hydroxyzine prescribing will not be long term. The expectation of much “as required” hydroxyzine prescribing and limited data to calculate duration in Denmark means estimating duration of prescribed therapy is challenging. Duration of treatment is this context is inherently difficult to decide, most use arbitrary definitions that may not accurately reflect real world use.

For the primary approach of estimating duration of hydroxyzine, we will assume a standard treatment regimen for each patient and prescription as if they were taking it with complete adherence. We will use a total daily dose 75mg hydroxyzine (base on the defined daily dose for hydroxyzine. For children under the age of 12, the following standard daily dosages will be applied: under 2 years 10mg; 2-5 years 15mg; 6-12 years 25mgs; 13-17 50mg. For example, a standard prescription consisting of 25mg strength tablets we will therefore divide the quantity of tablets/capsules per prescription by this standard regimen (i.e. 3) to provide the standard duration of therapy in days. We will measure trends in the average standard duration of therapy for prescriptions issued within each time period, before and after the date of the regulatory intervention.

As a secondary approach, we will attempt to divide patients prescribed hydroxyzine into one of three groups per time period: one-off users, sporadic users, and chronic users. One-off users will be defined as patients prescribed a single hydroxyzine prescription only. To define sporadic and chronic users we will calculate a possession ratio for each patient defined by using the number of days prescribed (or supplied) assuming a standard daily dose divided by the number of days between hydroxyzine prescriptions. We will

define sporadic users as patients with a hydroxyzine possession ratio of less than 1 standard day of therapy per 3 days. Patients with a hydroxyzine possession ratio of more than 1 standard day of therapy per 3 days will be defined as chronic users. One-off and sporadic users are mutually exclusive: “One-off” is a single prescription. “Sporadic” implies more than one prescription. We will then calculate time trends for the three groups per time period, before and after the date of the regulatory intervention.

5.8 OBJECTIVE 2: DEFINITIONS TO DETERMINE PRESCRIBERS COMPLIANCE WITH CARDIOVASCULAR CONTRAINDICATIONS AND RISK FACTORS

Objective 2 requires stratification of the hydroxyzine prescription rates by each of the following factors with Read, ICD and ICPC codes listed in Appendix 3 for each condition.

5.8.1 History of acquired or congenital QT interval prolongation

Hydroxyzine is prescribed to the contraindicated group in a time period if any of the codes for acquired or congenital QT interval prolongation are recorded prior to the first day of that time period. Once recorded they will continue to be considered contraindicated for all subsequent time periods.

5.8.2 History of cardiovascular disease

Hydroxyzine is prescribed to the contraindicated group in a time period if any of the codes for cardiovascular disease are recorded prior to the first day of that time period. Once recorded they will continue to be considered contraindicated for all subsequent time periods.

5.8.3 Recent significant electrolyte imbalance (hypokalaemia, hypomagnesaemia)

Hydroxyzine is prescribed to the contraindicated group in a time period if any of the primary or secondary care codes for (or biochemistry results indicative of) hypokalaemia and/or hypomagnesaemia are recorded in the 3 months prior to the first day of that time period.

5.8.4 Family history of sudden cardiac death

Hydroxyzine is prescribed to the contraindicated group in a time period if there is any recorded coding for family history of sudden cardiac death. Once recorded they will continue to be considered contraindicated for all subsequent time periods.

5.8.5 Recent symptomatic bradycardia

Hydroxyzine is prescribed to the contraindicated group in a time period if any of the codes for bradycardia are recorded in the 3 months prior to the first day of that time period. [Excluding where a pacemaker has been fitted?]

5.8.6 Recent concomitant use of drugs known to prolong the QT interval and/or induce Torsades de Pointes

Hydroxyzine is prescribed to the contraindicated group in a time period if there is co-prescribing of any drugs known to prolong the QT interval and/or induce Torsades de Pointes (see appendix). These will be divided into those likely to be short-term prescription (for example erythromycin or fluconazole) from those likely to be of long-term duration (for example sotalol or lithium) and analysed separately.

For the analysis, we will calculate the proportion of patients prescribed hydroxyzine in each time period who have each of the above factors.

5.9 OBJECTIVE 3: DEFINITIONS TO DETERMINE PRESCRIPTION PATTERNS OF ALTERNATIVE MEDICINES PRESCRIBED IN PATIENTS WHERE HYDROXYZINE HAS PREVIOUSLY BEEN PRESCRIBED

Objective 3 will describe trends in switch rates from hydroxyzine to each class of alternative medicine (codes for each class of alternative analgesics are listed in Appendix 2). A switch to an alternative class will be defined as discontinuation of hydroxyzine (as defined in section 5.7.4) followed by initiation a drug in the classes listed in section 3.3 within 92 days. Initiation is defined by the first prescription for a drug class for at least 92 days, i.e. continuing treatment with a drug class that started before hydroxyzine was discontinued is not regarded as a switch.

In addition, follow up time following discontinuation of hydroxyzine will be divided into successive 90 day intervals and, for each drug in the classes listed in section 3.3, we will count the number of patients who were prescribed it in each quarter.

5.10 STATISTICAL ANALYSES

5.10.1 Time period definition

The primary analysis will use quarterly time periods. For each year these will be defined by the following dates:

- 1st January to 31st March = Quarter 1
- 1st April to 30th June = Quarter 2
- 1st July to 30th September = Quarter 3
- 1st October to 31st December = Quarter 4

Data governance requirements may preclude reporting of strata containing fewer than 5 patients. If this occurs, we will either pool these strata with larger neighbouring groups (e.g. age 80+ with the 70-79 age group) or omit them. In either case, we will indicate in the report tables where data has been redacted.

5.10.2 Analytical approach

The proposed primary analysis will use interrupted time series regression to fit time trends to each series of time period data for each country. Using regression modelling we will evaluate:

1. The baseline slope before the intervention time point
2. The change in slope from the baseline trend to the post-intervention trend
3. The immediate change associated with the intervention time point

Before fitting all regression models, the data will be visualised graphically. The characteristics of the study cohort will be described at baseline. For objective 1, this will be done for overall hydroxyzine prescribing rates, hydroxyzine initiation rates and hydroxyzine discontinuation rates for all clinical indication and for individual clinical indications. For objective 2 this will be done for overall hydroxyzine prescribing rates in patients with a history of the following contraindications: patients with known acquired or congenital QT interval prolongation, a known risk factor for QT interval prolongation such as cardiovascular disease, significant electrolyte imbalance (hypokalaemia, hypomagnesaemia), family history of sudden cardiac death, significant bradycardia, or concomitant use of drugs known to prolong the QT interval and/or induce Torsades de Pointes. For objective 3, this will be done for people initiating drug classes listed in section 3.3 following discontinuation of hydroxyzine.

The effect of the intervention for each country will be represented either by a step function, or by a continuous linear function representing gradual implementation (interrupted time series analysis). This choice, and whether it is necessary to model any trends prior to the intervention time point, will be

decided on visual inspection of the data.[10] The analysis will be done by data source initially, and only pooled if the statistical models do not differ significantly between data sources.

5.10.3 Date of the regulatory intervention

For interrupted time series regression analysis, the date of the regulatory intervention will be pre-specified as 12 February 2015. The effects of the regulatory intervention may not occur immediately and may also be related to the final legally binding decision throughout the EU on 25 March 2015; however, as both dates fall within the same quarter there will be no sensitivity analysis around this. We will however evaluate whether any impact occurred in relation to the start of the referral (April 2014) on baseline trends. Even if prescribing patterns were in steady state before the intervention, and eventually reach a different steady state after it, the rates of transition between them may differ between countries. If there is no single measure of the effect of intervention on each outcome but modelling the pattern of change over time is required, we will used Joinpoint regression analysis. [11]

5.10.4 Autocorrelation

It is sometimes necessary to take account of autocorrelations in time series data. However, Wagner *et al* [12] found no autocorrelation in their prescribing data. We anticipate being able to use regression models that assume independent errors, but we will check that assumption using the Durbin Watson statistic.

5.11 LIMITATIONS

We acknowledge the limitations of each data source and the limitation of the missing data such as the limited sensitivity for definitions determining prescribers' compliance with cardiovascular contraindications and risk factors (for example acquired or congenital QT interval prolongation, recent significant electrolyte imbalance and family history of sudden cardiac death). As stated above we are unable to assess preoperative sedation as an indication for hydroxyzine. We will highlight these limitations in the report. Time to implementation of the regulatory intervention may significantly vary between data sources. If such an effect is observed following visual inspection of the data, an interrupted time series regression analysis with rescaled time and/or Joinpoint regression analysis will be used.[11] Furthermore, limitations in relation to other events since the referral procedure start date (April 2014) and the PRAC Recommendation (March 2015) may have impacted on prescribing/utilisation trends (such as media reports). Updating time dependent variables at the start of each quarterly interval may result in some misclassification early in a disease, although this is not thought likely to impact on the results.

5.12 DATA PROTECTION CONSTRAINTS

For Scotland, Denmark and PHARMO databases governance requirements may mean that data with fewer than 5 patients in a time period may not be made available publicly, or even to the study statistician. The need to aggregate data further, or to redact it, will be reviewed when the extent of the problem is known.

6 WORK PLAN/QUALITY ASSURANCE PLAN

The study will be under the control of a Steering Committee who will have overall responsibility for the conduct of the study. To ensure a consistent approach is adopted across all databases, the analysis will be performed by the same principal statistician who will be supported by the working-groups who will provide aggregate data for each time series.

6.1 STEERING GROUP

The study steering group will consist of one or more representatives from each of the main data sources. The membership of this group is detailed in Appendix 4.

6.2 ADVISORY GROUP

To help with analytical issues relating to regional prescribing variation, an advisory group will be convened consisting of clinical experts familiar with NSAID prescribing practices from each country.

6.3 QUALITY ASSURANCE

The steering committee will be responsible for the overall conduct of the study. An overarching Quality Assurance plan will be developed and submitted to the agency with the draft protocol. Quality control of statistical output will be done by independent code review. The Steering Committee will apply for the "ENCePP Study Seal" demonstrating adherence to the ENCePP Code of Conduct

6.4 INFORMATION GOVERNANCE

This study will be conducted according to best practice ethical and information governance frameworks. We will adhere to the governance and legal requirements that apply to each country and database used.

7 STUDY REPORT

The final report will provide a background review to the study, full methodologies used in the study, result interpretation and discussion, and details of conduct/management of the study. Full details of all statistical outputs will be given as appendices.

8 TIMETABLE

The proposed research is planned to complete within 18 months on the following time scale.

Months	**Mar-17 to May-18**	**Jun-18 to Aug-18**	**Sep-18 to Nov-18**	**Dec-18 to Feb-18**	**Mar-18 to May-19**	**Jun-19 to Aug-19**
Development of the study protocol						
Protocol agreed and approved Data assembled						
Data analysis (General approach)						
Modelling of time series data						
Interim analysis/report						
Drafting final report and publication						
Manuscript ready for submission						
Monthly research committee meetings						

9 APPENDICES.

Appendix 1: Clinical indications (code list to be finalised in the data extraction plan)

We will use the following codes to define the following licenced indications for hydroxyzine use:

1. *anxiety disorders:*
    - Read codes: *tbc*
    - ICD10 codes: *F40, F41*
    - ICPC codes: P01 – anxiety feelings, ICPC for anxiety disorders is P74
2. *Relief of pruritus (including that due to urticaria)*
    - Read codes: *tbc*
    - ICD10 codes: *L29*
    - ICPC codes: S98*,* S02
3. *Treatment of sleep disorders*
    - Read codes: *tbc*
    - ICD10 codes: *G47*
    - ICPC codes: P06

ICD10 = international classification of disease version 10 (Scotland/Denmark). ICPC = international classification of primary care codes (Netherlands). % is used to denote a wildcard meaning all codes below this level in the hierarchy are included.

Appendix 2: Codes used to determine alternative medicines prescribed in patients where hydroxyzine has previously been prescribed (code list to be finalised in the data extraction plan)

We will use the following codes to define the following alternative medicines to cover anxiety disorders, skin conditions, and sleep disorders:

1. *Other antihistamines*
    - BNF codes: 03.04.01
    - ATC codes: tbc
2. *Benzodiazepines*
    - BNF codes: 04.01.02
    - ATC codes: codes starting with N03AE,N05BA, N05CD, N05CF
3. *Others: Tricyclic antidepressents. Mirtazapine. Citalopram. (full list to be developed)*
    - BNF codes:
    - ATC codes:

Appendix 3: Contraindicated and high-risk groups (code list to be finalised in the data extraction plan)

We will use the following codes to define the following contraindicated and high-risk groups:

1. *History of acquired or congenital QT interval prolongation*

   Read codes:

   ICD10 codes: I45.8, I49.8, R94.3

   ICPC codes: K84.07

2. *History of cardiovascular disease*

   Read codes:

   ICD10 codes: G45.x, I01.0, I01.1, I01.2, I02.0, I05.x, I06.x, I07.x, I08.x, I09.x, I10.x, I11.x, I13.0, I13.00, I13.01, I13.2, I13.20, I13.21, I15.x, I20.x, I21.x, I22.x, I23.x, I24.1, I25.x, I26.x, I27.x, I30.x, I31.x, I32.x, I33.x, I34.x, I35.x, I36.x, I37.x, I38, I39.x, I40.x, I41.x, I42.x, I43.x, I44.x, I45.x, I46.1, I46.9, I47.x, I49.x, I50.x, I51.x, I52.x, I60.x, I61.x, I62.x, I63.x, I64, I69.x, I70.x, I71.x, I72.x, I73.x, I74.x, I77.x, I78.x, I79.x
   ICPC codes: K02, K75, K77, K82, K84 (except K84.07)

   Prescribing:

3. *Recent significant electrolyte imbalance (hypokalaemia, hypomagnesaemia)*

   Read codes:

   ICD10 codes: E87.6, E83.4

   ICPC codes: tbc

4. *Family history of sudden cardiac death*

   Read codes: Z82.41

   ICD10 codes: Z82.4

   ICPC codes: tbc

5. *Recent symptomatic bradycardia*

   Read codes:

   ICD10 codes: R00.1

   ICPC codes: tbc

ICD10 = international classification of disease version 10 (Scotland/Denmark). ICPC = international classification of primary care codes (Netherlands). % is used to denote a wildcard meaning all codes below this level in the hierarchy are included.

6. Recent concomitant use of drugs known to prolong the QT interval and/or induce Torsades de Pointes

Medicines known to prolong QT interval (to be classified as either of short or long-term duration) (ATC codes to be added)		**Medicines known to cause hypokalaemia (potentially increasing risk of Torsade de Pointes)** (ATC codes to be added)
Amifampridine	Methadone	Aminophylline
Amiodarone	Mizolastine	Amphotericin
Amisulpride	Moxifloxacin	Bambuterol
Anagrelide	Nilotinib	Beclometasone
Apomorphine	Ondansetron	Bedaquiline
Arsenic trioxide	Osimertinib	Bendroflumethiazide
Artemether	Paliperidone	Betamethasone
Artenimol	Palonosetron	Budesonide
Bosutinib	Panobinostat	Bumetanide
Cabozantinib	Pasireotide	Chlorothiazide
Ceritinib	Pazopanib	Chlortalidone
Chlorpromazine	Pentamidine	Clopamide
Citalopram	Pimozide	Cyclopenthiazide
Clarithromycin	Quinine	Deflazacort
Clomipramine	Ranolazine	Dexamethasone
Crizotinib	Ribociclib	Fludrocortisone
Dasatinib	Risperidone	Formoterol
Delamanid	Sildenafil	Furosemide
Disopyramide	Sorafenib	Hydrochlorothiazide
Domperidone	Sotalol	Hydrocortisone
Dronedarone	Sulpiride	Hydroflumethiazide
Droperidol	Sunitinib	Indacaterol
Efavirenz	Telavancin	Indapamide
Eribulin	Tetrabenazine	Ivabradine
Erythromycin	Tizanidine	Methylprednisolone
Escitalopram	Tolterodine	Metolazone
Fingolimod	Vandetanib	Olodaterol
Flecainide	Vardenafil	Prednisolone
Fluconazole	Vemurafenib	Prednisone
Fluphenazine	Venlafaxine	Salbutamol
Granisetron	Vinflunine	Salmeterol
Haloperidol	Voriconazole	Terbutaline
Inotuzumab ozogamicin	Zuclopenthixol	Theophylline
Lapatinib		Torasemide
Levomepromazine		Toremifene
Lithium		Triamcinolone
Lofexidine		Vilanterol
Mefloquine		Xipamide

Appendix 4: Steering Group Members

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10 REFERENCES

[1] European Medicines Agency. Annex III. Amendments to relevant sections of the summary of product characteristics and package leaflets. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Hydroxyzine_31/Position_provided_by_CMDh/WC500184901.pdf. (Accessed on 06 September 2017)

[2] European Medicines Agency. New restrictions to minimise the risks of effects on heart rhythm with hydroxyzine-containing medicines. http://www.ema.europa.eu/docs/en_GB/document_library=/Referrals_document/Hydroxyzine_31/Position_provided_by_CMDh/WC500184900.pdf. (Accessed on 06 September 2017)

[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyzine/human_referral_prac_000043.jsp&mid=WC0b01ac05805c516f (accessed 6th September 2017)

[4] Lee BH, Lee SH, Chu D, Hyun JW, Choe H, Choi BH, Jo SH. Effects of the histamine H(1) receptor antagonist hydroxyzine on hERG K(+) channels and cardiac action potential duration. Acta Pharmacol Sin. 2011;32(9):1128-37

[5] Alvarez-Madrazo S, McTaggart S, Nangle C, et al. Data Resource Profile: The Scottish National Prescribing Information System (PIS). Int J Epidemiol. 2016 Jun;45(3):714-715f. doi: 10.1093/ije/dyw060. Epub 2016 May 10. No abstract available.

[6] Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a Tool in Epidemiology. Eur J Epidemiol 2014;29(8):541-9. doi: 10.1007/s10654-014-9930-3.

[7] Pottegård A, Schmidt SA, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2016 Oct 27. DOI: 10.1093/ije/dyw213

[8] Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: A Review of Content, Data Quality, and Research Potential. Clin Epidemiol 2015;7:449-90. doi: 10.2147/CLEP.S91125.

[9] Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun;44(3):827-36.

[10] Penning-van Beest FJ1, Termorshuizen F, Goettsch WG, Klungel OH, Kastelein JJ, Herings RM. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. Eur Heart J 2007; 28(2): 154–159. DOI: 10.1093/eurheartj/ehl391.

[11] Joinpoint Trend Analysis Software. https://surveillance.cancer.gov/joinpoint/ (Accessed on 30 May 2017)

[12] Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002 Aug;27(4):299-309.