05Nov19

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

Final Study Report

University of Dundee Led Consortium

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Contents

ABSTRACT

Background: Antihistamines such as hydroxyzine, may be commonly prescribed agents across Europe for the management of skin disorder, sleep disorders and anxiety. In February 2015, a European Medicines Agency (EMA) referral procedure concluded that hydroxyzine containing products were pro-arrythmogenic and that contraindications, warnings, and changes to the product information, including direct healthcare professional communication (DHPC) were required to be implemented across the EU.

Objectives: The aim of the study was to evaluate the impact of the risk minimisation measures implemented in 2015 to manage the pro-arrythmogenic risks of hydroxyzine containing medicinal products in Denmark, Netherlands, England and Scotland.

Method: Drug utilisation studies assessing hydroxyzine containing medical products covering the regulatory intervention in February 2015. Quarterly time series analyses measuring: the prevalence of hydroxyzine initiation and discontinuation in the population as a whole: the prevalence of hydroxyzine initiation in patients with cardiovascular disease, electrolyte disturbance, bradycardia, family history of sudden cardiac death and concomitant use of drugs that may prolong the QT interval and/or induce Torsade De Pointes; and initiation of other antihistamines, benzodiazepines and other antidepressant medications (tricyclic antidepressants, mirtazapine, selective serotonin reuptake inhibitors) in patients who discontinued hydroxyzine containing medical products. Statistical significance testing was performed using interrupted time series regression.

Results: The 2015 EMA regulatory intervention had no significant impact on hydroxyzine initiation as a whole in Denmark or the Netherlands. The intervention was associated with a significant: immediate fall in hydroxyzine initiation per 100,000 in England (-12.05, 95%CI -18.47 to -5.63) and Scotland (19.01, 95%CI -26.99 to -11.02); and change to a negative trend in hydroxyzine initiation per 100,000 per quarter in England (-1.72, 95%CI -2.69 to -0.75) and Scotland (-2.378, 95%CI -3.318 to -1.438). The regulatory intervention was associated with a significant: immediate rise in hydroxyzine discontinuation per 100 in England (3.85, 95%CI 0.44 to 7.24) and an immediate fall in Denmark (-2.91, 95%CI -5.33 to -0.48). The regulatory intervention was associated with significant falls in initiation in patients with cardiovascular disease in England and Scotland and in patients with concomitant use of drugs known to prolong the QT interval in England, Scotland and Denmark. No data were available to evaluate the impact of the regulatory intervention in patients with a family history of sudden cardiac death and only limited data were available for hydroxyzine initiation in patients with electrolyte disturbance and bradycardia. The regulatory intervention was associated with no significant switching to other antihistamines, benzodiazepines or other antidepressant medicines following hydroxyzine discontinuation.

Conclusion: The 2015 EMA referral was associated with significant reductions in overall hydroxyzine initiation in England and Scotland only, and limited impact on discontinuation in all countries. There was no significant evidence to suggest unintended consequences of switching to other antihistamines, benzodiazepines or other antidepressant medicines overall.

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 was to measure the impact of the risk minimisation measures, which drew attention to new contraindications, warnings, and other changes to the product information. We analysed 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 provide these trends by age, gender and by indication for hydroxyzine.

Our objectives fell into three areas:

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

We included hydroxyzine containing medicinal products with Anatomical Therapeutic Chemical (ATC) codes: N05BB01, N05BB51, and BNF (British National Formulary) codes 3040102. This identified:

- Systemic products formulated as tablets or capsules for oral administration (group 1)
- Suppositories for rectal administration (group 2)
- Solutions for intravenous or intramuscular injection (group 3)

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

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

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

This was first done for all indications and then by individual indications, age and gender. Secondary analysis calculated prescription patterns for each hydroxyzine-containing group (i.e. group 1 tablets/capsules, group 2 rectal suppositories and group 3 intramuscular/intravenous) for any indication and then by indication, age and gender.

3.2 OBJECTIVE 2: DETERMINING PRESCRIBERS COMPLIANCE WITH RECOMMENDATIONS

We assessed 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, by calculating prescription patterns in overall hydroxyzine prescribing rates and hydroxyzine initiation rates among patients with a 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 was 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 and/or induce Torsade de Pointes

For overall hydroxyzine prescribing this was first done for all patients exposed and then by indication, age and gender. Secondary analysis calculated prescription patterns for each hydroxyzine-containing group (i.e. group 1 tablets/capsules, group 2 rectal suppositories and group 3 intramuscular/intravenous) for any indication and then by indication, age and gender.

3.3 Objective 3: Determine prescription patterns of alternative medicines prescribed in patients where hydroxyzine has previously been prescribed

Among patients who discontinued hydroxyzine therapy we calculated prescription patterns in the proportions who subsequently initiated treatment with other therapies for:

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

Please see Appendix 1 for list of codes used to identify these drugs. These included 1) other prescribed antihistamine-containing medicinal products, 2) benzodiazepine-containing medicinal products, and 3) other sedative containing medicinal products.

4 Data source summaries

Four validated population data sources[5-10] were 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,[6] readily allows linkage of drug exposures to outcomes in the form of ICD-10 diagnoses registered in connection with inpatient and outpatient hospital contacts.[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, but we used only practices outside Scotland, so data were used from England, Wales and Northern Ireland: for the purposes of this report, these will be referred to as England. The data has been collected since 1987, covers about 7% of the UK population and is broadly generalisable to the whole UK population.[9] For this study, data was 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, THE 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 were 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). These data can be linked on a patient-level using probabilistic linkage to other databases. Data on indication and contraindications were 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. ICPC codes can be mapped to ICD codes. [10] Data linked with the GP Database was available from 2007 up to 2016.

5 STUDY METHODS

Population-based longitudinal studies were conducted using these four databases using this common protocol (EU PAS (post-authorisation studies) Register number EUPAS26363).

5.1 OVERVIEW

Individual patient data sets were assembled in each country. The list of variables included in the study are defined in this document. Some of these variables were not available in every country. The different database structures and coding systems used by each country meant that different logic was used to calculate each of the variables listed within. These were reviewed for consistency between countries. To further improve consistency a high-level data extraction plan was used, for each country to adhere to. An aggregate data set was prepared in each country. This consisted of a full cross classification of the data by all the stratification variables, and by time period. This data set was aggregated further and forwarded to the central study statistician providing the minimum count per time period containing greater than or equal to 5 patients per cell to meet with local data protection and disclosure control requirements.

5.2 Study Period

The study start period varied by data source and the fact that patients were required to have at least one year of observation (lookback period) prior to inclusion in the cohort.

5.3 Study population

The study population consisted of all patients registered within each data source at any time during the study period. The start of follow-up for a patient was defined as 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 was the latest of the study period start date (dependent on each data source), the 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). A patient's end of follow-up was the date of the first occurrence of the following: death (all databases); end of study period (varies between countries); end of registration (end of registration would not significantly affect data from Denmark and Scotland because they use national data that captures patients moving within the health system). A patient was included for analysis in a time period if the first and last day both lay between the patient's index date and their last follow up date, so the analyses only included patients who are observable for the entire time period.

5.4 Outcome variables

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

5.5 Stratification variables

Most stratification variables in the study were time dependent and were evaluated at the start of each time period. Gender and age was used to stratify hydroxyzine prescription rates for all three objectives.

Age was classified as 0-17, 18-29, 30-39, 40-49, 50-59, 60-69, 70-79 or 80+.

Read, ICD or ICPC codes were used to classify licenced indications: *anxiety disorders, skin disorders and sleep disorders.* The classification was based on any record dated before the end of the time period. If a patient had a history of the indication of interest they were included in the analysis for that indication and it is possible that patients may appear more once when examining different indications.

5.6 Objective 1: Definitions to determine prescription patterns of hydroxyzine containing products

5.6.1 Objective 1.1: Hydroxyzine initiation rates

Hydroxyzine initiation was defined as a prescription for hydroxyzine with no exposure to hydroxyzine in the preceding 92 days. The denominator was 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 was the number of these patients initiating hydroxyzine in the time period.

5.6.2 Objective 1.2: Overall hydroxyzine prescribing rates by patients

For overall hydroxyzine prescribing rates, the denominator was defined as the number of observable patients on the first day of the time period (both hydroxyzine users and non-users). The numerator was defined as the number of these patients with any prescription for hydroxyzine in the time period. The

exception was for Denmark where the denominator was the number of patients present in the cohort on 1st January each year.

5.6.3 Objective 1.3: Overall hydroxyzine prescribing rates by prescriptions

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

5.6.4 Objective 1.4: Hydroxyzine discontinuation rates

Discontinuation was defined as the number of patients with a prescription for hydroxyzine with no exposure to hydroxyzine in the 92 days following the date of that hydroxyzine prescription. This definition did not include 92 days plus an estimated exposure duration. The denominator was the number of patients prescribed hydroxyzine in the time period. The numerator was the number of these patients discontinuing.

5.6.5 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 was calculated as (strength x quantity summed over all prescriptions in the episode) / (length of episode including unexposed days). This allowed the dose to be calculated from strength and quantity. Further details of defining exposure episodes are contained in Appendix 2.

5.6.6 Objective 1.6: Duration of hydroxyzine

From clinical experience we suspected that most hydroxyzine prescribing was not long term. For the primary approach of estimating duration of hydroxyzine, we assumed a standard treatment regimen for each patient and prescription as if they were taking it with complete adherence. We used a total daily dose 75mg hydroxyzine based 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 years 50mg. For example, a standard prescription consisting of 25mg strength tablets we divided the quantity of tablets/capsules per prescription by this standard regimen (i.e. 3) to provide the standard duration of therapy in days. We measured 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 attempted to divide patients prescribed hydroxyzine into one of three groups per time period: one-off users, sporadic users, and chronic users. Using hydroxyzine treatment episodes, one-off users were defined as patients prescribed a single hydroxyzine prescription only in the treatment episode. To define sporadic and chronic users we calculated 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 within a treatment episode. We defined sporadic users as patients with a hydroxyzine possession ratio of less than 1 standard day of therapy per 3 days within the treatment episode. Patients with a hydroxyzine possession ratio of more than 1 standard day of therapy per 3 days were defined as chronic users within the treatment episode. Patients were allocated to either one-off, sporadic or chronic if the treatment episode occurred within a quarter. We then calculated time trends for the three groups per time period, before and after the date of the regulatory intervention. Further details of defining exposure episodes are contained in Appendix 2.

5.7 Objective 2: Determining prescribers compliance with cardiovascular contraindications and risk factors

Objective 2 required stratification of the hydroxyzine prescription rates by each of the following factors with Read, ICD and ICPC codes listed in Appendix 1 for each condition.

5.7.1 History of cardiovascular disease

Hydroxyzine was prescribed to the contraindicated group in a time period if any of the codes for cardiovascular disease were recorded prior to the end date of that time period. Once a diagnosis was recorded, patients continued to be considered contraindicated for all subsequent time periods.

5.7.2 Recent significant electrolyte imbalance (hypokalaemia, hypomagnesaemia)

Hydroxyzine was prescribed to the contraindicated group in a time period if any of the codes for recent significant electrolyte imbalance (hypokalaemia, hypomagnesaemia) were recorded in the 3 months prior to the first day of that time period.

5.7.3 Family history of sudden cardiac death

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

5.7.4 Recent symptomatic bradycardia

Hydroxyzine was prescribed to the contraindicated group in a time period if any of the codes for bradycardia were recorded in the 3 months prior to the first day of that time period.

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

Hydroxyzine was prescribed to the contraindicated group in a time period if there is recent concomitant prescribing of any drugs known to prolong the QT interval and/or induce Torsades de Pointes (please see Appendix 1 for further details). Recent concomitant prescribing was defined as the number of patients having initiated hydroxyzine who have also been prescribed a drugs known to prolong the QT interval and/or induce Torsades de Pointes within the previous 90 days.

5.8 Objective 3: Determine prescription patterns of alternative medicines prescribed in patients where hydroxyzine has previously been prescribed

Objective 3 determined drug utilisation and prescription patterns over time for other medicines when hydroxyzine had been discontinued.

A switch to an alternative class was defined as those patients who discontinued hydroxyzine (as defined in section 5.6.4) and who then initiated a drug in the classes listed in section 3.3. Initiation of an alternative drug in the classes listed in section 3.3 was defined as the first prescription of a drug in that class prescribed within 92 days following the date of the last hydroxyzine prescription.

5.9 Statistical analyses

5.9.1 Time period definition

The primary analysis used quarterly time periods. For each year these were 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 precluded reporting of strata containing fewer than 5 patients. When this occurred we omitted them. We indicate in the report tables where data has been redacted.

5.9.2 Analytical approach

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

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

Before fitting all regression models, the data was visualised graphically. The characteristics of the study cohort was described at baseline. For objective 1, this was done for overall hydroxyzine prescribing rates, hydroxyzine initiation rates and hydroxyzine discontinuation rates for any clinical indication and for individual clinical indications. For objective 2 this was done for overall hydroxyzine prescribing rates in patients with 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 was done for patients initiating drug classes listed in section 3.3, following discontinuation of hydroxyzine.

The effect of the intervention for each country was 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 period, was decided on visual inspection of the data.[11] The analysis was done and is reported by datasource.

All of the aggregated datasets provided by each country consisted of ratios, in most cases a proportion of patients, for a set of consecutive quarters. The purpose of the analyses was to measure any change in trends over time after the pre-specified date of the regulatory intervention, February 2015, and was achieved by fitting interrupted time series (ITS) models with a joint point at this date. They were parameterised in such a way that one parameter estimated the change in slope after vs before the time period at which the intervention occurred (the coefficient of a time variable counting the number of quarters since the intervention and set to 0 before it), and another estimated any step change at the join point (the coefficient of a variable set to 1 after the intervention and 0 before it).[11] In some data sets there was evidence of discontinuities at other times, in either absolute rates or their slopes. These were not the subject of this study and therefore the range of data was trimmed to periods immediately before and after February 2015 when trends were approximated to be linear.

Preliminary analyses using binomial models revealed substantial over dispersion in the data relative to that expected in binomial proportions with very large denominators. We therefore assumed normal error distributions and fitted trends using weighted linear regression, the weights being the denominators in each proportion. We found no increase in the magnitude of residuals with increasing fitted values and therefore did not transform the data to log units for analysis.

All analyses were carried out using SAS V9.4.

5.9.3 Date of the regulatory intervention

For interrupted time series regression analysis, the date of the regulatory intervention was pre-specified as 12 February 2015.

5.9.4 Autocorrelation

We checked for autocorrelation in the data using the Durbin Watson statistic.

5.9.5 Guide to interpreting the trend results

In the results section, the prevalence of each drug prescribing pattern will be summarised as the proportion at the beginning of the availability of each data source to the end of each data source and these quarterly data points will be presented in the subsequent figures. However, the results of the trend analysis may be based upon a different numbers of pre- and/or post-intervention data points due to observable differences in trend occurring at different points in the pre- and/or post-intervention period, inclusion of which may have introduce bias into the time series analysis models and violated the linear assumptions. Thus the time periods used in the interrupted time series regression models are visualised as shaded areas within each figure provided to differentiate that from all time periods. Terminology used to describe the trends are:

- No trend = no statistically significant increase or decrease in the prevalence of prescribing over sequential data points detected
- Positive trend = a statistically significant increase in the prevalence of prescribing over sequential data points detected
- Negative trend = a statistically significant decrease in the prevalence of prescribing over sequential data points detected

Of note, changes in the slope post-intervention is relative to the baseline slope. For example, no significant change in trend post-intervention means that the trend after the intervention was the same as that before. Similarly, a positive trend post-intervention when the pre-intervention trend was negative means the trend is slowing or has reversed.

Further details of the methodology are contained within Appendix 2.

6 RESULTS

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

Output tables, figures and ITS regression results for objective 1 are shown in Appendix 3 to 10.

6.1.1 Hydroxyzine initiation rates for any indication

Trends in the prevalence of hydroxyzine initiation among Denmark, the Netherlands, England and Scotland are shown in figure 1. Different start periods are presented due to the final availability of data between countries. Between the study periods available for analysis, the number of patients initiating hydroxyzine-containing medicinal products per 100,000: in Denmark remained fairly stable from 23.5 (2010Q1) to 24.7 (2018Q1); in the Netherlands fell from 34.4 (2009Q2) to 25.4 (2017Q4); in England (CPRD) fell from 35.9 (2009Q1) to 30.8 (2018Q1); and in Scotland fell from 91.5 (2010Q1) to 58.9 (2018Q2).

Interrupted time series regression of hydroxyzine initiation rates

In Denmark, there was a positive trend in hydroxyzine initiation before the regulatory intervention (table 6.1.1). The regulatory intervention was associated with no statistically significant immediate absolute fall in initiation (-1.66, 95%CI -4.93 to 1.61 per 100,000) and no statistically significant change in initiation trend post-intervention compared to baseline.

In England, there was a positive trend in hydroxyzine initiation before the regulatory intervention. The regulatory intervention was associated with a statistically significant immediate absolute fall in initiation of -12.05 (95%CI -18.47 to -5.63 per 100,000) and a change to a negative trend in initiation of -1.72 (95%CI -2.69 to -0.75) per 100,000/quarter post-intervention compared to baseline.

In the Netherlands, there was no trend in hydroxyzine initiation before the regulatory intervention. The regulatory intervention was associated with no statistically significant immediate absolute change in initiation and no statistically significant change in trend in initiation post-intervention compared to baseline.

In Scotland, there was a positive trend in hydroxyzine initiation before the regulatory intervention. The regulatory intervention was associated with a statistically significant immediate absolute fall in initiation of -19.01 (95%CI -26.99 to -11.02) per 100,000with a change to a negative trend in initiation -2.38 (95%CI -3.32 to -1.44) per 100,000/quarter post-intervention compared to baseline.

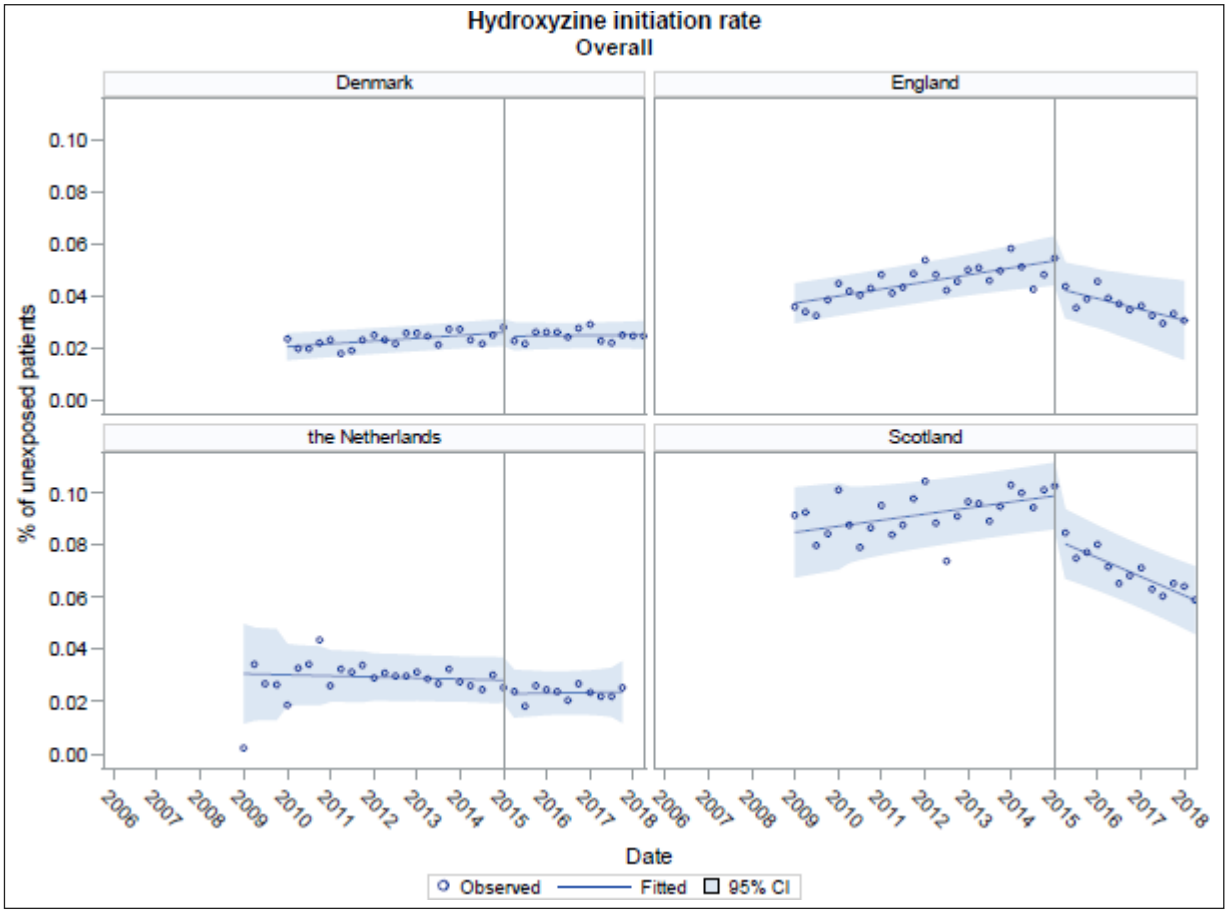

Figure 1. Hydroxyzine initiation rate overall.

6.1.2 Hydroxyzine exposure rates by patients for any indication

Trends in the prevalence of hydroxyzine exposure rates by patients among Denmark, the Netherlands, England and Scotland are shown in figure 2. Between the study periods available for analysis, the proportion of patients exposed to hydroxyzine-containing medicinal products per 100,000: in Denmark rose from 29.3 (2010Q1) to 42.1 (2018Q1); in the Netherlands fell slightly from 43.2 (2009Q2) to 40.8 (2017Q4); in England (CPRD) rose from 32.8 (2009Q1) to 56.7 (2018Q1); and in Scotland rose slightly from 103.7 (2010Q1) to 107.6 (2018Q2).

Interrupted time series regression of hydroxyzine exposure rates by patients

In Denmark, there was a positive trend in hydroxyzine exposed patients before the regulatory intervention (table 6.1.2). The regulatory intervention was associated with no statistically significant immediate absolute change in exposed patients but was associated with a change to a negative trend in exposed patients of -0.31 (95%CI -0.44 to -0.18) per 100,000/quarter post-intervention compared to baseline.

In England, there was a positive trend in hydroxyzine exposed patients before the regulatory intervention. The regulatory intervention was not associated with a statistically significant immediate absolute fall in exposed patients but was associated with a change to a negative trend in exposed patients of -3.08 (95%CI -3.82 to -2.33) per 100,000/quarter compared to baseline.

In the Netherlands, there was a positive trend in hydroxyzine exposed patients before the regulatory intervention. The regulatory intervention was associated with no statistically significant immediate absolute change in exposed patients and no statistically significant change in trend in exposed patients compared to baseline.

In Scotland, there was a positive trend in hydroxyzine exposed patients before the regulatory intervention. The regulatory intervention was associated with no statistically significant immediate absolute change in exposed patients but was associated with a change to a negative trend in exposed patients of -4.55 (95%CI -6.56 to -2.55) per 100,000/quarter compared to baseline.

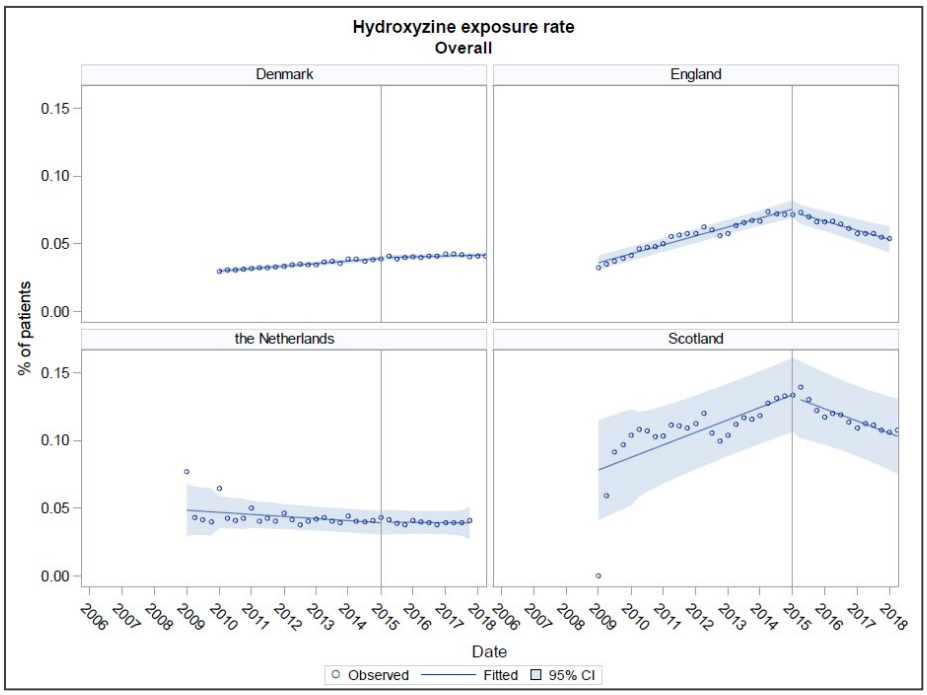

Figure 2. Hydroxyzine exposure rate overall.

6.1.3 Hydroxyzine prescribing rates by prescriptions for any indication

Trends in the prescription rates for hydroxyzine-containing medicinal products per 1000 patients among Denmark, the Netherlands, England and Scotland are shown in figure 3. Between the study periods available for analysis, the prescribing rates by patients to hydroxyzine-containing medicinal products per 1000: in Denmark remained stable at 0.8; in the Netherlands rose from 2.7 (2009Q2) to 3.3 (2017Q4); in England (CPRD) rose from 1.2 (2009Q1) to 1.8 (2018Q1); and in Scotland this fell from 3.4 (2010Q1) to 2.9 (2018Q2).

Interrupted time series regression of hydroxyzine prescribing rates per 1000 patients

In Denmark, there was a positive trend in hydroxyzine prescribing rates before the regulatory intervention (table 6.1.3). The regulatory intervention was associated with no statistically significant immediate absolute change in prescribing rates and no statistically significant change in trend compared to baseline.

In England, there was a positive trend in hydroxyzine prescribing rates before the regulatory intervention. The regulatory intervention was associated with a statistically significant immediate absolute fall in prescribing rates of -0.22 (95%CI -0.36 to -0.07), and was associated with a change to a negative trend in prescribing rates of -0.09 (95%CI -0.12 to -0.07) per 1000/quarter post-intervention compared to baseline.

In the Netherlands, there was no trend in hydroxyzine prescribing rates before the regulatory intervention. The regulatory intervention was associated with no statistically significant immediate absolute change in prescribing rates and no statistically significant change in trend in prescribing rates post-intervention compared to baseline.

In Scotland, there was a positive trend in hydroxyzine prescribing rates before the regulatory intervention. The regulatory intervention was associated with a statistically significant immediate absolute fall in prescribing rates of -0.36 (95%CI -0.71 to -0.02) per 1000 and with a change to a negative trend in prescribing of -0.13 (95%CI -0.17 to -0.09) per 1000/quarter post-intervention compared to baseline.

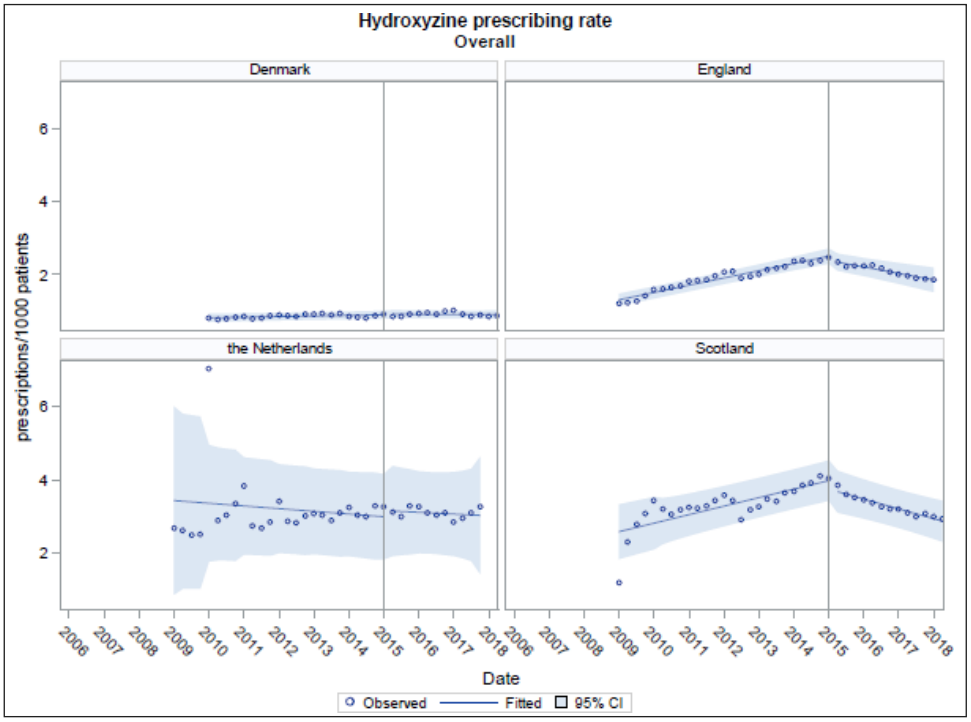

Figure 3. Hydroxyzine prescribing rate overall.

6.1.4 Hydroxyzine discontinuation rates for any indication

Trends in hydroxyzine discontinuation among Denmark, the Netherlands, England and Scotland are shown in figure 4. Between the study periods available for analysis, the discontinuation rates for hydroxyzine-containing medicinal products per 100: in Denmark rose from 33.7 (2010Q1) to 36.9 (2018Q1); in the Netherlands fell from 27.1 (2009Q2) to 4.7 (2017Q4); in England (CPRD) fell from 29.4 (2009Q1) to 21.6 (2018Q1); and in Scotland this fell from 27.5 (2010Q1) to 25.4 (2018Q2).

Interrupted time series regression of hydroxyzine discontinuation rates

In Denmark, there was a positive trend in hydroxyzine discontinuation before the regulatory intervention (table 6.1.4). The regulatory intervention was associated with a statistically significant immediate absolute fall in discontinuation of -2.91 (95%CI -5.33 to -0.48) per 100 and a change to a negative trend in discontinuation of -0.43 (95%CI -0.71 to -0.14) per 100/quarter post-intervention compared to baseline.

In England, there was a negative trend in hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with a statistically significant immediate absolute rise in hydroxyzine discontinuation of 3.85 (95%CI 0.44 to 7.24) per 100/quarter and a change to a negative trend in discontinuation of -0.56 (95%CI -1.09 to -0.02) per 100/quarter post-intervention compared to baseline.

In the Netherlands, there was a negative trend in hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with no statistically significant immediate absolute change in discontinuation and no statistically significant change in hydroxyzine discontinuation trend compared to baseline.

In Scotland, there was a negative trend in hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with no statistically significant immediate absolute change in discontinuation and no statistically significant change in hydroxyzine discontinuation trend compared to baseline.

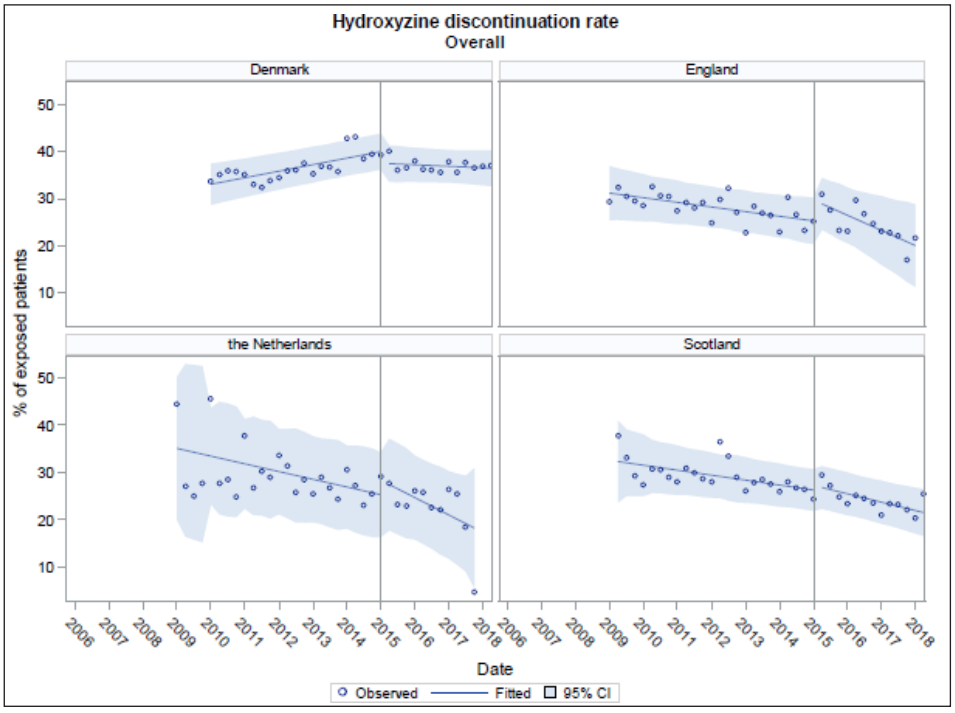

Figure 4. Hydroxyzine discontinuation rate overall.

6.1.5 Dose of hydroxyzine for any indication

Trends in the mean daily dose of hydroxyzine-containing medicinal products among Denmark, the Netherlands, England and Scotland are shown in figure 6. Between the study periods available for analysis, the mean daily dose of hydroxyzine prescriptions remained stable: in Denmark at around 72mg; in the Netherlands at around 74mg; in England at around 72mg; and in Scotland at around 74mg.

Interrupted time series regression of hydroxyzine mean daily dose

In Denmark, there was a positive trend in the mean daily dose of hydroxyzine before the regulatory intervention (table 6.1.5). The regulatory intervention was associated with a statistically significant immediate increase in the mean daily dose hydroxyzine of 0.34 (95%CI 0.06 to 0.62) mg and with a change to a negative change in trend of -0.04 (95%CI -0.08 to -0.01) mg/quarter post-intervention compared to baseline.

In England, there was a negative trend in the mean daily dose of hydroxyzine before the regulatory intervention. The regulatory intervention was not associated with a statistically significant immediate absolute rise in the mean daily dose of hydroxyzine but was associated with a change to a positive trend of 0.36 (95%CI 0.24 to 0.48) mg/quarter post-intervention compared to baseline.

In the Netherlands, there was no trend in the mean daily dose of hydroxyzine before the regulatory intervention. The regulatory intervention was associated with a statistically significant immediate absolute fall in the mean daily dose of hydroxyzine of -0.75 (95%CI -1.45 to -0.05) mg and a change to a positive trend of 0.28 (95%CI 0.18 to 0.38) mg/quarter post-intervention compared to baseline.

In Scotland, there was a negative trend in the mean daily dose of hydroxyzine before the regulatory intervention. The regulatory intervention was associated with a statistically significant immediate rise in the mean daily dose of hydroxyzine of 0.50 (95%CI 0.06 to 0.95) mg and a change to a positive trend of 0.25 (95%CI 0.19 to 0.30) mg/quarter post-intervention compared to baseline.

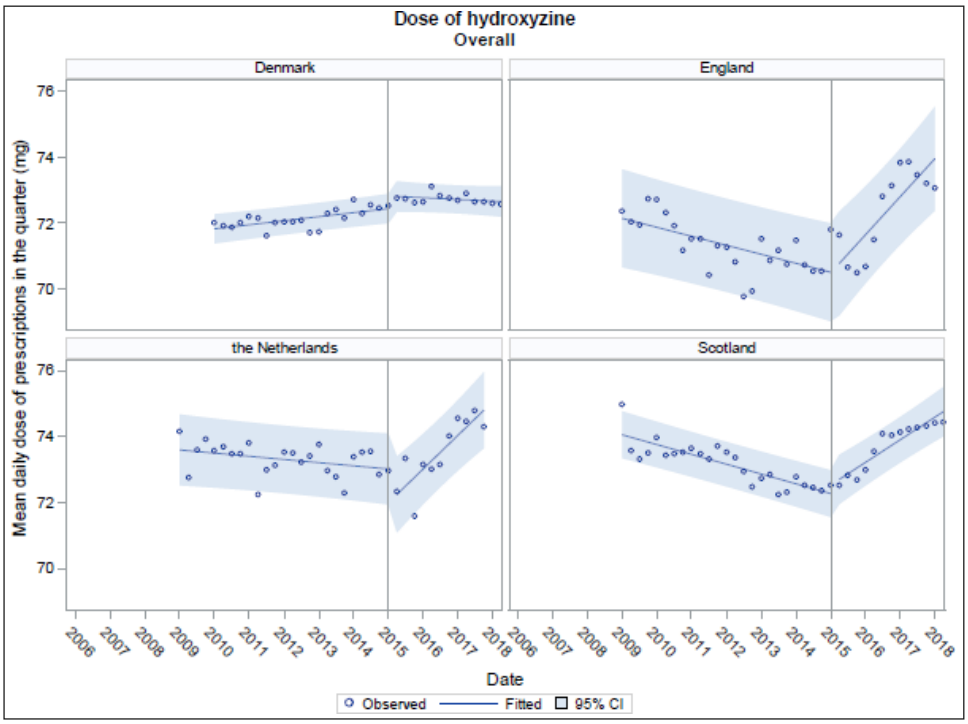

Figure 5. Trends in the mean daily dose of hydroxyzine per country.

6.1.6 Duration of hydroxyzine therapy for any indication

Trends in the duration of prescriptions for hydroxyzine-containing medicinal products among Denmark, the Netherlands, England and Scotland are shown in figure 5. Between the study periods available for analysis, the duration of hydroxyzine prescriptions: in Denmark increased from 21 days (2010Q1) to 31 days (2018Q1); in the Netherlands fell from 6 days (2009Q2) to 4 days (2017Q4); in England (CPRD) fell from 15 days (2009Q1) to 12 days (2018Q1); and in Scotland fell from 16 days (2010Q1) to 15 days (2018Q2).

Interrupted time series regression of hydroxyzine duration

In Denmark, there was no trend in the duration of hydroxyzine prescriptions before the regulatory intervention (table 6.1.6). The regulatory intervention was not associated with a statistically significant immediate change in the duration of hydroxyzine prescriptions and was not associated with a significant trend in the duration of hydroxyzine prescriptions post-intervention compared to baseline.

In England, there was a negative trend in the duration of hydroxyzine prescriptions before the regulatory intervention. The regulatory intervention was not associated with a statistically significant immediate absolute rise in the duration of hydroxyzine prescriptions and no significant change trend in the duration of hydroxyzine prescriptions post-intervention compared to baseline.

In the Netherlands, there was a negative trend in the duration of hydroxyzine containing prescriptions before the regulatory intervention. The regulatory intervention was not associated with a statistically significant immediate absolute change in the duration of hydroxyzine prescriptions and no statistically significant change in trend post-intervention compared to baseline.

In Scotland, there was a negative trend in the duration of hydroxyzine prescriptions before the regulatory intervention. The regulatory intervention was not associated with a statistically significant immediate change in the duration of hydroxyzine prescriptions and no statistically significant change in trend in the duration of hydroxyzine prescriptions post-intervention compared to baseline.

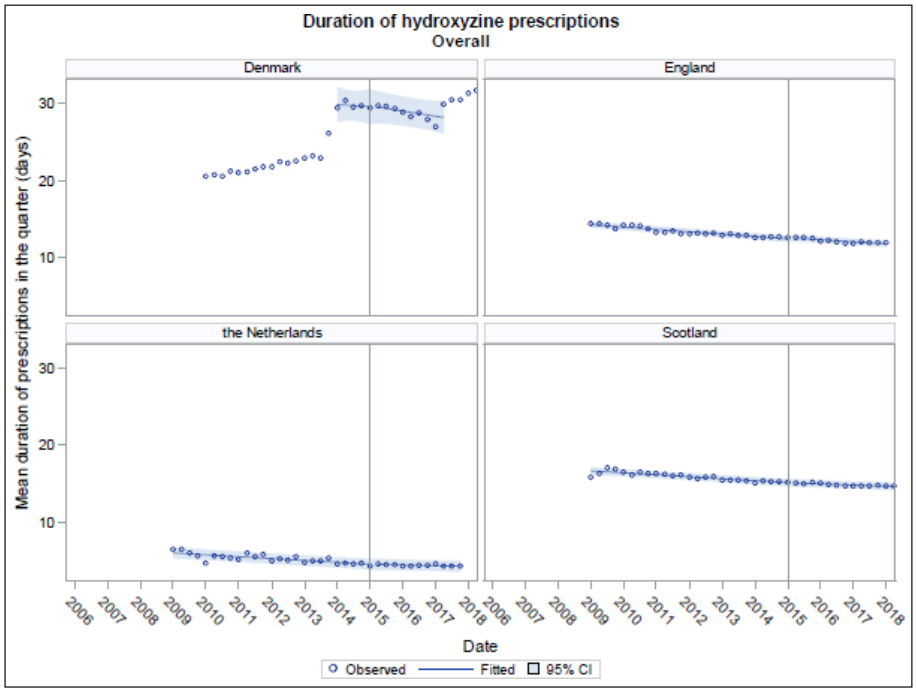

Figure 6. Duration of hydroxyzine prescription

Table 6.1.1. Interrupted time series regression results for trends in overall hydroxyzine initiation rates in each country.

Country	*Before February 2015 (per 100,000/quarter)*	*Change after February 2015 (per 100,000/quarter)*	*Change in first quarter after February 2015 (per 100,000)*
Denmark	0.269 (0.098, 0.441), p=0.003	-0.224 (-0.612, 0.164), p=0.247	-1.661 (-4.932, 1.609), p=0.308
England	0.677 (0.463, 0.891), p=<.001	-1.720 (-2.694,-0.746), p=0.001	-12.05 (-18.47,-5.631), p=<.001
The Netherlands	-0.102 (-0.400, 0.197), p=0.492	0.164 (-0.699, 1.026), p=0.701	-5.079 (-10.92, 0.766), p=0.086
Scotland	0.582 (0.205, 0.959), p=0.003	-2.378 (-3.318,-1.438), p=<.001	-19.01 (-26.99,-11.02), p=<.001

Table 6.1.2. Interrupted time series regression results for trends in overall hydroxyzine exposure rates in each country.

Country	*Before February 2015 (per 100,000/quarter)*	*Change after February 2015 (per 100,000/quarter)*	*Change in first quarter after February 2015 (per 100,000)*
Denmark	0.459 (0.400, 0.518), p=<.001	-0.309 (-0.442,-0.176), p=<.001	0.387 (-0.736, 1.509), p=0.487
England	1.539 (1.375, 1.703), p=<.001	-3.076 (-3.824,-2.327), p=<.001	-2.342 (-7.274, 2.591), p=0.341
The Netherlands	-0.384 (-0.681,-0.087), p=0.013	0.314 (-0.544, 1.172), p=0.461	0.900 (-4.917, 6.717), p=0.755
Scotland	2.306 (1.502, 3.110), p=<.001	-4.553 (-6.558,-2.548), p=<.001	-5.843 (-22.87,11.189), p=0.490

Table 6.1.3. Interrupted time series regression results for trends in overall hydroxyzine prescribing rates in each country.

Country	*Before February 2015 (per 1000 /quarter)*	*Change after February 2015 (per 1000 /quarter)*	*Change in first quarter after February 2015 (per 1000)*
Denmark	0.004 (0.000, 0.008), p=0.029	-0.005 (-0.013, 0.003), p=0.227	0.011 (-0.060, 0.081), p=0.760
England	0.050 (0.045, 0.055), p=<.001	-0.094 (-0.115,-0.072), p=<.001	-0.215 (-0.357,-0.073), p=0.004
The Netherlands	-0.018 (-0.059, 0.022), p=0.359	0.006 (-0.110, 0.123), p=0.911	0.175 (-0.616, 0.966), p=0.655
Scotland	0.058 (0.042, 0.075), p=<.001	-0.126 (-0.167,-0.085), p=<.001	-0.363 (-0.709,-0.017), p=0.040

Table 6.1.4. Interrupted time series regression results for trends in overall hydroxyzine discontinuation rates in each country.

Country	*Before February 2015 (per 100/quarter)*	*Change after February 2015 (per 100/quarter)*	*Change in first quarter after February 2015 (per 100)*
Denmark	0.346 (0.211, 0.481), p=<.001	-0.425 (-0.710,-0.139), p=0.005	-2.905 (-5.328,-0.481), p=0.020
England	-0.246 (-0.375,-0.116), p=<.001	-0.558 (-1.093,-0.023), p=0.042	3.852 (0.439, 7.264), p=0.028
The Netherlands	-0.409 (-0.710,-0.108), p=0.009	-0.512 (-1.435, 0.412), p=0.267	2.560 (-3.660, 8.781), p=0.408
Scotland	-0.263 (-0.413,-0.112), p=0.001	-0.181 (-0.529, 0.167), p=0.297	794.4 (-2082.0, 3670.9), p=0.578

Table 6.1.5. Interrupted time series regression results for trends in mean daily dose in overall hydroxyzine prescriptions in each country.

Country	*Before February 2015 (mg/quarter)*	*Change after February 2015 (mg/quarter)*	*Change in first quarter after February 2015 (mg)*
Denmark	0.031 (0.016, 0.045), p=<.001	-0.043 (-0.077,-0.010), p=0.013	0.338 (0.055, 0.621), p=0.021
England	-0.068 (-0.106,-0.030), p=0.001	0.357 (0.235, 0.479), p=<.001	0.336 (-0.608, 1.279), p=0.474
The Netherlands	-0.024 (-0.052, 0.004), p=0.088	0.279 (0.180, 0.379), p=<.001	-0.747 (-1.448,-0.046), p=0.037
Scotland	-0.074 (-0.093,-0.056), p=<.001	0.246 (0.193, 0.298), p=<.001	0.504 (0.063, 0.945), p=0.026

Table 6.1.6. Interrupted time series regression results for trends in the mean duration of hydroxyzine prescriptions in each country.

Country	*Before February 2015 (days/quarter)*	*Change after February 2015 (days/quarter)*	*Change in first quarter after February 2015 (days)*
Denmark	-0.072 (-0.630, 0.486), p=0.779	-0.095 (-0.697, 0.508), p=0.733	0.021 (-2.124, 2.165), p=0.983
England	-0.076 (-0.087,-0.066), p=<.001	0.009 (-0.025, 0.043), p=0.591	0.168 (-0.096, 0.432), p=0.205
The Netherlands	-0.062 (-0.080,-0.043), p=<.001	0.040 (-0.025, 0.104), p=0.222	0.043 (-0.413, 0.499), p=0.850
Scotland	-0.063 (-0.076,-0.051), p=<.001	0.025 (-0.010, 0.061), p=0.160	0.014 (-0.288, 0.315), p=0.928

6.2 OBJECTIVE 2: DETERMINING PRESCRIBERS COMPLIANCE WITH CONTRAINDICATIONS AND RISK FACTORS

Output tables, figures and ITS regression results for objective 2 are shown in Appendix 11 to 16.

6.2.1 Hydroxyzine initiation for any indication in patients with cardiovascular disease

Trends in the prevalence of hydroxyzine initiation among Denmark, the Netherlands, England and Scotland in patients with cardiovascular disease are shown in figure 7. Between the study periods available for analysis, hydroxyzine initiation in patients with CVS disease per 100,000: in Denmark fell from 81.1 (2010q1) to 62.8 (2018q1); in the Netherlands fell from 92.5 (2009Q2) to 39.9 (2017Q4); in England (CPRD) fell slightly from 96.5 (2009q1) to 91.1 (2018q1); and in Scotland this fell from 161.4 (2010Q1) to 102.7 (2018Q2).

Interrupted time series regression of hydroxyzine initiation in patients with cardiovascular disease

Interrupted time series regression results for hydroxyzine initiation in patients with cardiovascular disease are shown in the appendix. In Denmark, there was a no trend in hydroxyzine initiation in patients with cardiovascular disease before the regulatory intervention (table 6.2.1). The regulatory intervention was associated with a non-statistically significant immediate fall in initiation in patients with cardiovascular disease (-7.22, 95%CI -18.11 to 3.67 per 100,000) with no statistically significant change in initiation trend post-intervention compared to baseline.

In England, there was a positive trend in hydroxyzine initiation in patients with cardiovascular disease before the regulatory intervention. The regulatory intervention was associated with a statistically significant immediate absolute fall in initiation in patients with cardiovascular disease (-36.47, 95%CI -59.42 to -13.51 per 100,000) with a change to a negative trend (-3.20, 95%CI -6.75 to -0.36 per 100,000/quarter) post-intervention compared to baseline.

In the Netherlands, there was a negative trend in hydroxyzine initiation in patients with cardiovascular disease before the regulatory intervention. The regulatory intervention was associated with a non-statistically significant immediate fall in initiation in patients with cardiovascular disease (-5.73, 95%CI -22.81 to 11.35 per 100,000) with no statistically significant change in initiation trend compared to baseline.

In Scotland, there was a positive trend in hydroxyzine initiation in patients with cardiovascular disease before the regulatory intervention. The regulatory intervention was associated with a statistically significant immediate absolute fall in initiation in patients with cardiovascular disease of -46.16, 95%CI -69.98 to -22.34 per 100,000)) and a change to a negative trend (-3.79, 95%CI -6.60 to -0.98 per 100,000/quarter) post-intervention compared to baseline.

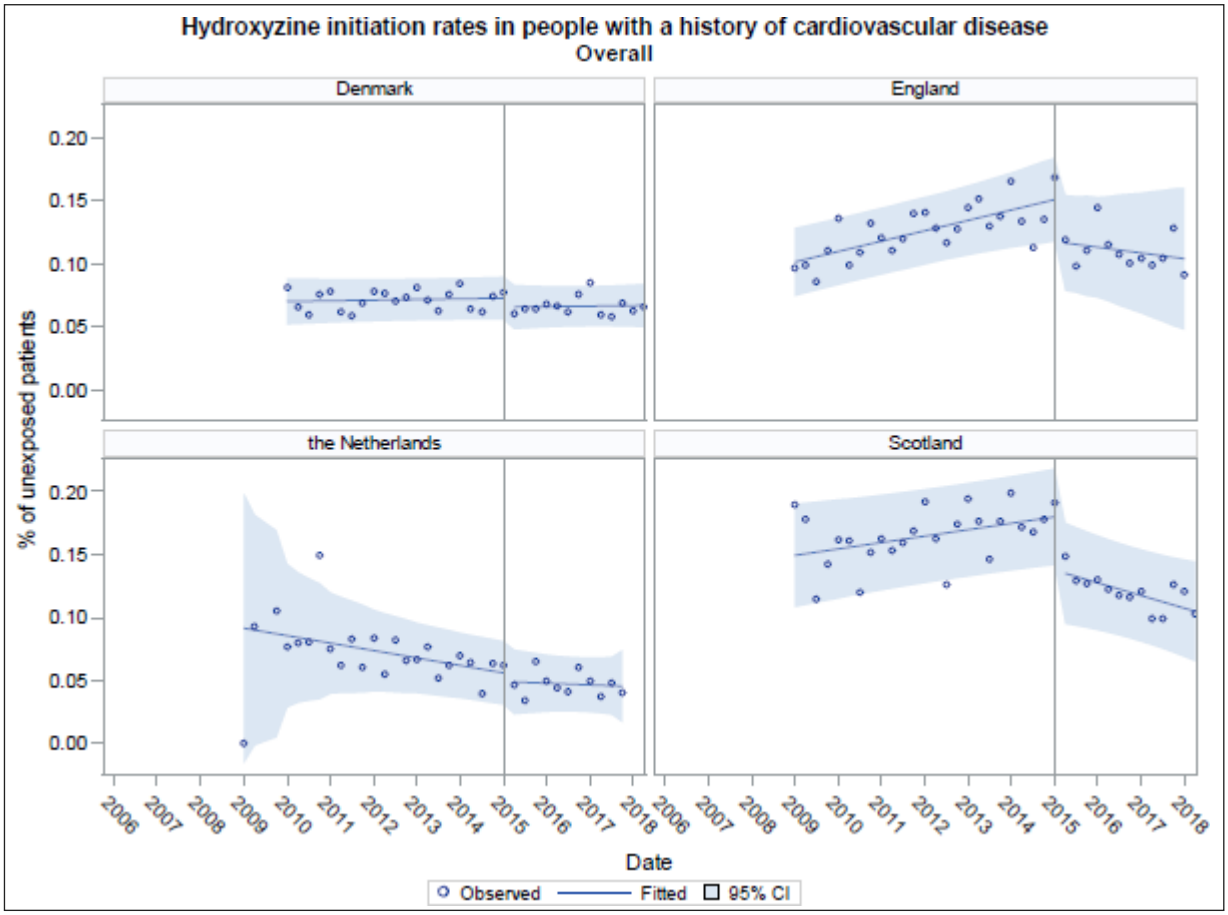

Figure 7. Hydroxyzine initiation rates in patients with cardiovascular disease

6.2.2 Hydroxyzine initiation in patients with recent significant electrolyte imbalance

Trends in the prevalence of hydroxyzine initiation among Denmark, the Netherlands, England and Scotland in patients with recent significant electrolyte imbalance are shown in figure 8. The cell count for these data were extremely low and typically less than 5 and frequently zero or could not be presented due to the low cell count that makes it difficult for the data and regression output to be truly informative.

Interrupted time series regression of hydroxyzine initiation in patients with recent electrolyte imbalance

Interrupted time series regression results for hydroxyzine initiation in patients with electrolyte imbalance are shown in the appendix. In Denmark, there was a no trend in hydroxyzine initiation in patients with electrolyte imbalance before the regulatory intervention (table 6.2.2). The regulatory intervention was not associated with a statistically significant immediate fall in initiation in patients with electrolyte imbalance and no statistically significant change in initiation trend post-intervention compared to baseline.

In Scotland, there was no trend in hydroxyzine initiation in patients with electrolyte imbalance before the regulatory intervention. The regulatory intervention was not associated with a statistically significant immediate absolute change in initiation in patients with electrolyte imbalance and no statistically significant change in initiation trend post-intervention compared to baseline.

Parameter estimates from England and the Netherlands are not available due to the low cell count and zero counts.

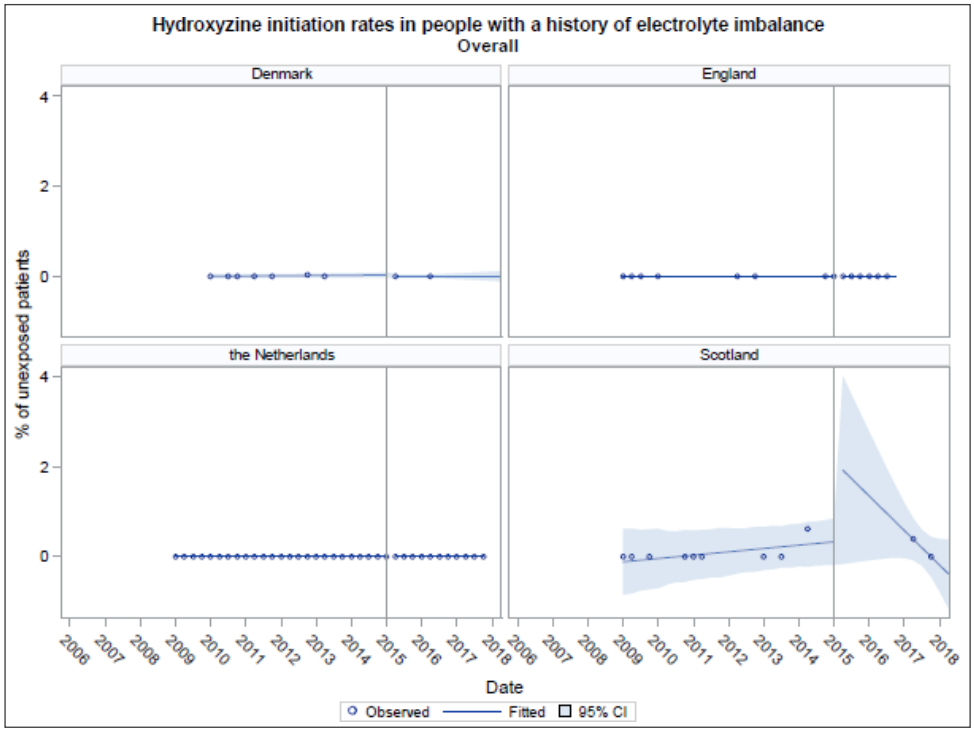

Figure 8. Hydroxyzine initiation rates in patients with recent history electrolyte imbalance.

6.2.3 Hydroxyzine initiation in patients with a family history of sudden cardiac death

No patients with a family history of sudden cardiac death were identified within the data sources.

6.2.4 Hydroxyzine initiation in patients with recent symptomatic bradycardia

Trends in the prevalence of hydroxyzine initiation among Denmark, the Netherlands, England and Scotland in patients with recent bradycardia are shown in figure 9. The cell count for these data were extremely low in all countries that make it difficult for the data and regression output to be truly informative.

Interrupted time series regression of hydroxyzine initiation in patients with recent bradycardia

Interrupted time series regression results for hydroxyzine initiation in patients with recent bradycardia are shown in the appendix. There are no parameter estimates available for Denmark, the Netherlands, England and Scotland due to the frequent low cell count or zero initiation of hydroxyzine in patients with bradycardia.

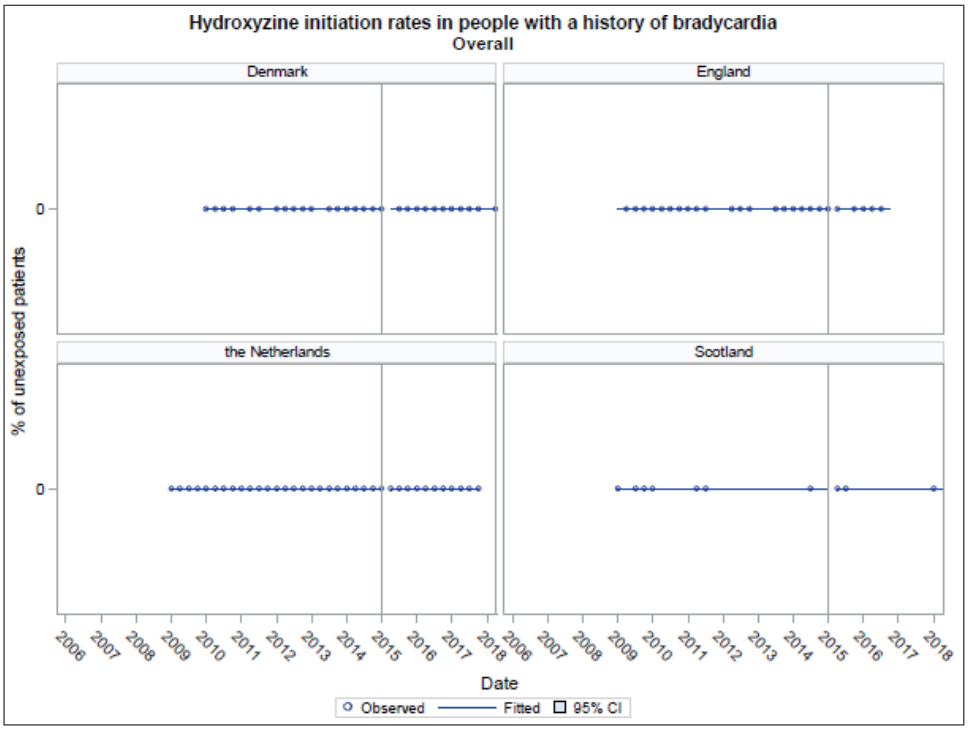

Figure 9. Hydroxyzine initiation in patients with a recent history of bradycardia.

6.2.5 Hydroxyzine initiation in patients with concomitant use of drugs known to prolong the QT interval

Trends in prevalence of hydroxyzine initiation in patients with concomitant use of drugs known to prolong the QT interval are shown in figure 10. The prevalence of hydroxyzine initiation with concomitant use of drugs known to prolong the QT interval per 100,000: in Denmark rose from 101.1 (2010Q1) to 122.0 (2018Q1); in the Netherlands fell from 121.0 (2009Q2) to 69.7 (2017Q4); in England fell from 127.0 (2009Q1) to 97.5 (2016Q4); in Scotland fell from 230.0 (2010Q1) to 138.9 (2108Q2).

Interrupted time series regression of hydroxyzine initiation in patients with concomitant use of drugs known to prolong the QT interval/induce Torsade De Pointes

All parameter estimates are shown in the appendix. In Denmark, there was a positive trend in hydroxyzine initiation in patients with concomitant use of drugs known to prolong the QT interval before the regulatory intervention (table 6.2.3). The regulatory intervention was not associated with a statistically significant immediate absolute change in hydroxyzine initiation but was associated with a change to a negative trend of -1.69 (95%CI -3.36 to -0.02) per 100,000/quarter compared to baseline.

In England, there was a positive trend in hydroxyzine initiation in patients with concomitant use of drugs known to prolong the QT interval before the regulatory. The regulatory intervention was associated with a statistically significant immediate absolute fall in hydroxyzine initiation of -57.06 (95%CI -84.69 to -29.44) per 100,000 and was associated with a change to a negative trend of -8.51 (95%CI -16.24 to -0.77) pre 100,000/quarter post-intervention compared to baseline.

In the Netherlands, there was a negative trend in hydroxyzine initiation in patients with concomitant use of drugs known to prolong the QT interval before the regulatory. The regulatory intervention was associated with a no significant immediate absolute change in initiation in patients with concomitant use of drugs known to prolong the QT and no change in trend post-intervention compared to baseline.

In Scotland, there was a positive trend in hydroxyzine initiation in patients with concomitant use of drugs known to prolong the QT interval before the regulatory intervention. The regulatory intervention was associated with a statistically significant immediate absolute fall in hydroxyzine initiation of -50.10 (95%CI -71.07 to -29.12) per 100,000 and a change to a negative trend in initiation of -7.45 (95%CI -9.92 to -4.98) per 100,000/quarter post-intervention compared to baseline.

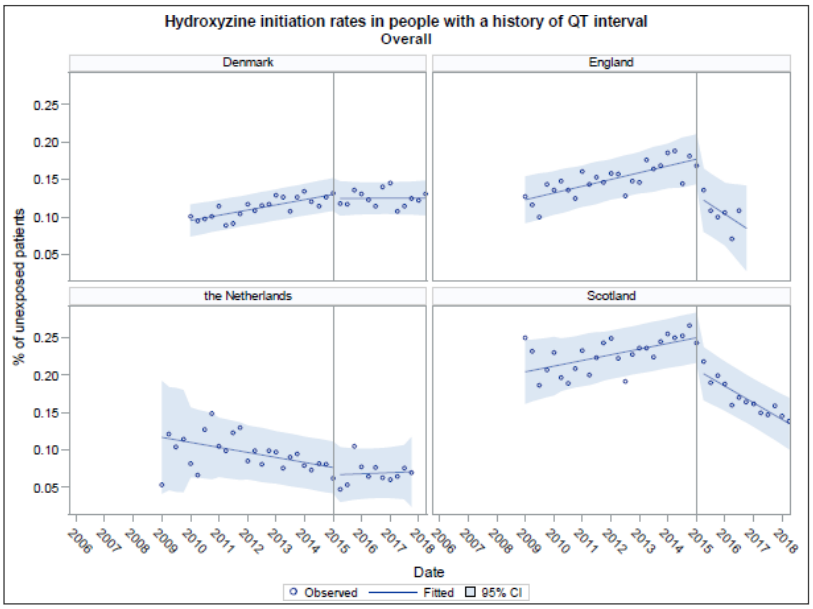

Figure 10. Hydroxyzine initiation with concomitant use of drugs known to prolong the QT interval.

Table 6.2.1. Interrupted time series regression results for trends in overall hydroxyzine initiation in patients with a history of cardiovascular disease.

Country	*Before February 2015 (per 100,000/quarter)*	*Change after February 2015 (per 100,000/quarter)*	*Change in first quarter after February 2015 (per 100,000)*
Denmark	0.130 (-0.457, 0.717), p=0.654	-0.022 (-1.308, 1.263), p=0.972	-7.219 (-18.11, 3.671), p=0.186
England	2.059 (1.299, 2.820), p=<.001	-3.196 (-6.751, 0.359), p=0.076	-36.47 (-59.42,-13.51), p=0.003
The Netherlands	-1.478 (-2.607,-0.349), p=0.012	1.144 (-1.258, 3.547), p=0.339	-5.732 (-22.81,11.348), p=0.499
Scotland	1.273 (0.251, 2.294), p=0.016	-3.786 (-6.595,-0.977), p=0.010	-46.16 (-69.98,-22.34), p=<.001

Table 6.2.2. Interrupted time series regression results for trends in overall hydroxyzine initiation in patients with a history of electrolyte imbalance.

Country	*Before February 2015 (per 100,000/quarter)*	*Change after February 2015 (per 100,000/quarter)*	*Change in first quarter after February 2015 (per 100,000)*
Denmark	1.443 (-1.870, 4.755), p=0.314	-1.443 (-12.66, 9.777), p=0.754	-27.42 (-86.59,31.744), p=0.287
England	Not available	Not available	Not available
The Netherlands	Not available	Not available	Not available
Scotland	18.605 (-5.016,42.227), p=0.105	-210.9 (-437.6,15.780), p=0.064	1575.3 (-509.4,3660.0), p=0.117

Table 6.2.3. Interrupted time series regression results for trends in overall hydroxyzine initiation in patients with drugs known to prolong the QT interval.

Country	*Before February 2015* *(per 100/quarter)*	*Change after February 2015* *(per 100/quarter)*	*Change in first quarter after February 2015* *(per 100)*
Denmark	1.739 (1.024, 2.454), p=<.001	-1.690 (-3.358,-0.022), p=0.047	-7.025 (-20.97, 6.920), p=0.312
England	2.258 (1.447, 3.069), p=<.001	-8.506 (-16.24,-0.769), p=0.032	-57.06 (-84.69,-29.44), p=<.001
The Netherlands	-1.675 (-2.855,-0.495), p=0.007	2.048 (-1.359, 5.454), p=0.230	-7.886 (-31.14,15.367), p=0.495
Scotland	1.899 (0.951, 2.848), p=<.001	-7.446 (-9.916,-4.975), p=<.001	-50.10 (-71.07,-29.12), p=<.001

6.2.6 Stratification by age, gender, indication and product (formulation) type

Detailed information on the prevalence of hydroxyzine initiation and prescribing among each country for objective 1 and objective 2 by age, gender, indication and type of product are shown in the figures and respective tables in the appendix (supplementary tables in Appendix 4-9 and Appendix 12-15, and supplementary figure in Appendix 3 and 11).

For objective 1 and objective 2, trends in the proportion of patients prescribed, initiating and discontinuing hydroxyzine-containing medicinal products by age and their slopes in all countries were similar to overall hydroxyzine initiation trends and slopes, but changes were typically more prominent in the older age groups in whom the prevalence of hydroxyzine exposure was greater than in younger age groups. Trends and slopes by gender were also similar to overall trends and slopes, although exposure to hydroxyzine was greater in women than in men.

In all countries, trends in the prescribing of hydroxyzine-containing medical products were driven oral products and no other formulation was identified. The most frequent type of prescribing was one-off prescribing. Of the indications examined the most common indication for hydroxyzine was for the treatment of skin disorders in all countries.

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

Output tables, figures and ITS regression results for objective 3 are shown in Appendix 17 to 19.

6.3.1 Switching to other antihistamines following hydroxyzine discontinuation

Trends in the prevalence of initiation in switching to other antihistamines following hydroxyzine discontinuation among Denmark, the Netherlands, England and Scotland are shown in figure 11. Between the study periods available for analysis, the rates of switching to other antihistamines following hydroxyzine discontinuation per 100: in Denmark fell from 8.6 (2010Q1) to 6.8 (2018Q1); in the Netherlands fell from 12.3 (2009Q2) to 1.9 (2017Q2); in England (CPRD) fell from 6.4 (2009Q1) to 5.3 (2018Q1); and in Scotland rose from 7.6 (2010Q1) to 8.5 (2018Q2).

Interrupted time series regression of switching to other antihistamines

In Denmark, there was a no trend in switching to other antihistamines following hydroxyzine discontinuation before the regulatory intervention (table 6.3.1). The regulatory intervention was associated with a non-statistically significant immediate rise in switching to other antihistamines following hydroxyzine discontinuation with no statistically significant change in switching trend compared to baseline.

In England, there was a no trend in switching to other antihistamines following hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with a non-statistically significant immediate rise in switching to other antihistamines following hydroxyzine discontinuation and a no significant change in switching trend post-intervention compared to baseline.

In the Netherlands, there was a negative trend in switching to other antihistamines following hydroxyzine discontinuation before the regulatory intervention of -0.20 (95%CI -0.31 to -0.09) per 100/quarter. The regulatory intervention was associated with a non-statistically significant immediate rise in switching to other antihistamines following hydroxyzine discontinuation and no significant change in switching trend post-intervention compared to baseline.

In Scotland, there was a no trend in switching to other antihistamines following hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with a non-statistically significant immediate rise in switching to other antihistamines following hydroxyzine discontinuation and a no significant change in switching trend post-intervention compared to baseline.

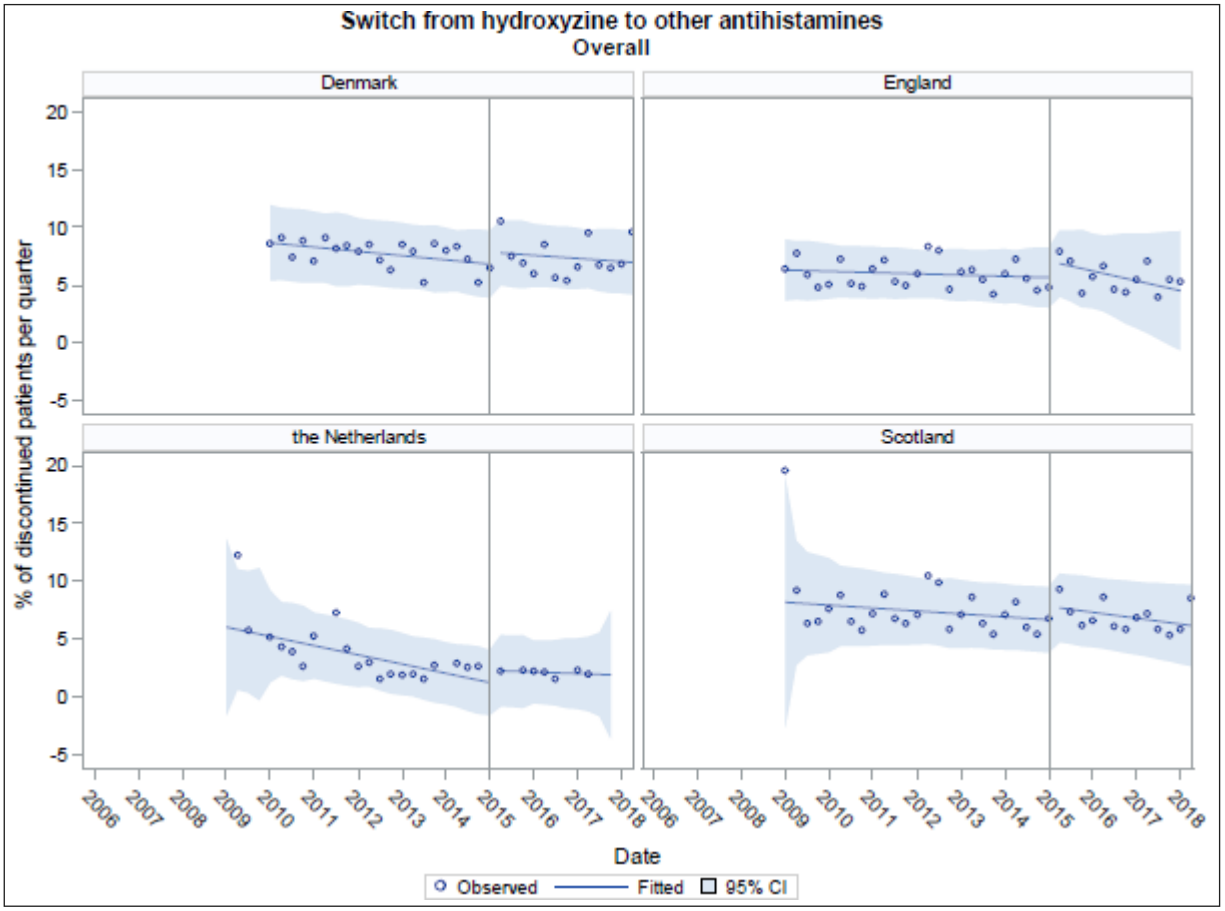

Figure 11. Switch from hydroxyzine to other antihistamines overall.

6.3.2 Switching to benzodiazepines following hydroxyzine discontinuation

Trends in the prevalence of initiation in switching to benzodiazepines following hydroxyzine discontinuation among Denmark, the Netherlands, England and Scotland are shown in figure 12. Between the study periods available for analysis, the rates of switching to benzodiazepines following hydroxyzine discontinuation per 100: in Denmark fell from 11.3 (2010Q1) to 8.3 (2018Q1); in the Netherlands fell from 3.1 (2010Q2) to 1.6 (2015Q3); in England (CPRD) fell from 2.2 (2009Q1) to 1.7 (2017Q3); and in Scotland fell from 3.2 (2010Q1) to 2.5 (2018Q2).

Interrupted time series regression of switching to benzodiazepines

In Denmark, there was a negative trend in switching to benzodiazepines following hydroxyzine discontinuation before the regulatory intervention of -0.08% (95%CI -0.14 to-0.01) per quarter (table 6.3.2). The regulatory intervention was associated with a non-statistically significant immediate rise in switching to benzodiazepines following hydroxyzine discontinuation and no significant change in switching trend compared to baseline.

In England, there was no trend in switching to benzodiazepines following hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with a non-statistically significant immediate rise in switching to benzodiazepines following hydroxyzine discontinuation and no significant change in trend in switching post-intervention compared to baseline.

In the Netherlands, there was a negative trend in switching to benzodiazepines following hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with no statistically significant immediate change in switching to benzodiazepines following hydroxyzine discontinuation and no significant change in switching trend post-intervention compared to baseline.

In Scotland, there was a negative trend in switching to benzodiazepines following hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with a non-statistically significant immediate rise in switching to benzodiazepines following hydroxyzine discontinuation and no significant change in switching trend compared to baseline.

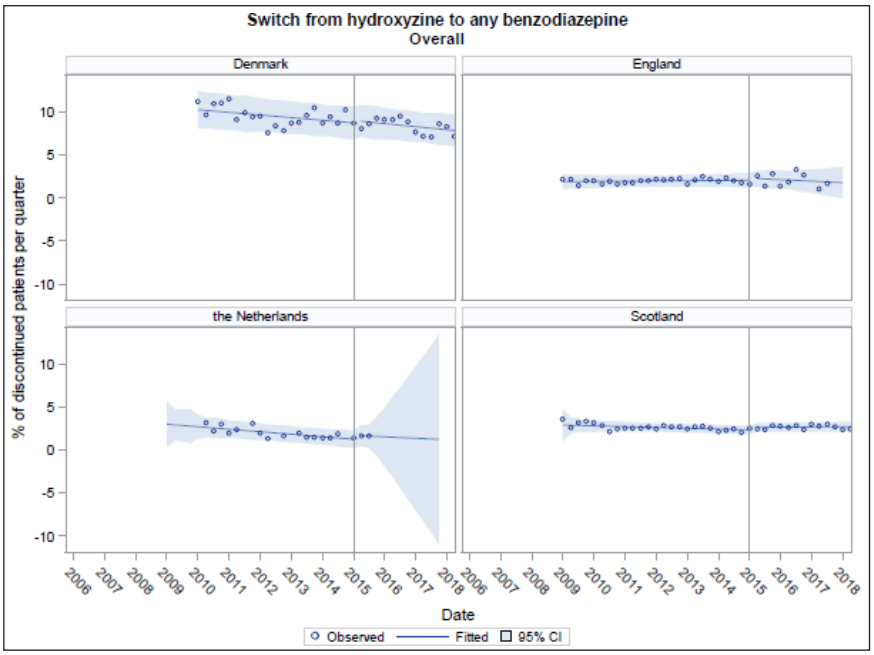

Figure 12. Switch from hydroxyzine to benzodiazepines overall.

6.3.3 Switching to other medications following hydroxyzine discontinuation

Trends in the prevalence of initiation in switching to other medications (tricyclic antidepressants, mirtazapine, SSRIs) following hydroxyzine discontinuation among Denmark, the Netherlands, England and Scotland are shown in figure 16. Between the study periods available for analysis, the rates of switching to other medications following hydroxyzine discontinuation per 100: in Denmark remained fairly stable at 18.3 (2010Q1) and 19.3 (2018Q1); in England (CPRD) fell from 4.8 (2009Q1) to 1.8 (2018Q1); and in Scotland rose from 4.5 (2010Q1) to 5.2 (2018Q2).

Interrupted time series regression of switching to other medications

In Denmark, there was no trend in switching to other medications following hydroxyzine discontinuation before the regulatory intervention (table 6.3.3). The regulatory intervention was associated with a non-statistically significant immediate fall in switching to other medications following hydroxyzine discontinuation and no significant change in switching trend post-intervention compared to baseline.

In England, there was no trend in switching to other medications following hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with a non-statistically significant immediate rise in switching to other medications following hydroxyzine discontinuation and no significant change in switching trend post-intervention compared to baseline.

In the Netherlands, there was a no trend in switching to other medications following hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with a non-statistically significant immediate rise in switching to other medications following hydroxyzine discontinuation and no significant change in switching trend post-intervention compared to baseline.

In Scotland, there was a no trend in switching to other medications following hydroxyzine discontinuation before the regulatory intervention. The regulatory intervention was associated with a non-statistically significant immediate absolute fall in switching to other medications following hydroxyzine discontinuation and no significant change in switching trend post-intervention compared to baseline.

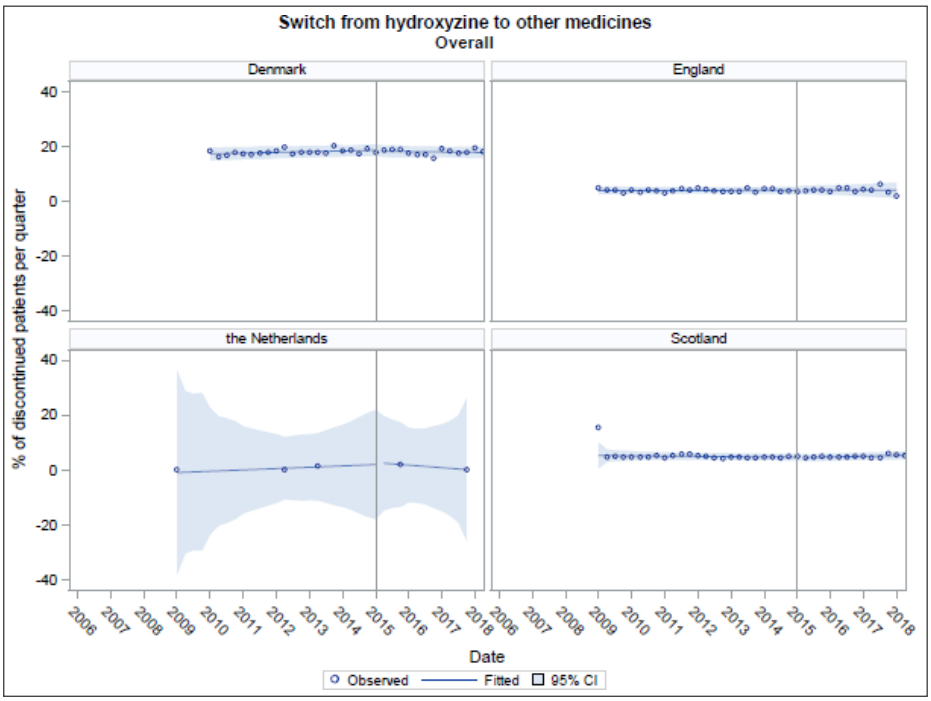

Figure 13. Switch from hydroxyzine to other medications overall.

Table 6.3.1. Interrupted time series regression results for trends in switching to other antihistamines.

Country	*Before February 2015 (per 100/quarter)*	*Change after February 2015 (per 100/quarter)*	*Change in first quarter after February 2015 (per 100)*
Denmark	-0.092 (-0.193, 0.009), p=0.074	0.024 (-0.161, 0.208), p=0.796	1.058 (-0.706, 2.823), p=0.231
England	-0.027 (-0.092, 0.038), p=0.401	-0.187 (-0.486, 0.112), p=0.212	1.237 (-0.587, 3.061), p=0.177
The Netherlands	-0.200 (-0.308,-0.092), p=<.001	0.165 (-0.232, 0.562), p=0.400	1.216 (-1.084, 3.516), p=0.285
Scotland	-0.063 (-0.158, 0.031), p=0.183	-0.065 (-0.300, 0.171), p=0.580	1.092 (-0.790, 2.975), p=0.246

Table 6.3.2. Interrupted time series regression results for trends in switching to benzodiazepines.

Country	*Before February 2015 (per 100/quarter)*	*Change after February 2015 (per 100/quarter)*	*Change in first quarter after February 2015 (per 100)*
Denmark	-0.076 (-0.144,-0.009), p=0.027	-0.013 (-0.135, 0.110), p=0.835	0.263 (-0.906, 1.431), p=0.650
England	0.007 (-0.014, 0.027), p=0.498	-0.050 (-0.175, 0.076), p=0.425	0.184 (-0.423, 0.791), p=0.540
The Netherlands	-0.073 (-0.112,-0.033), p=0.002	0.031 (-1.232, 1.293), p=0.959	0.481 (-0.493, 1.456), p=0.307
Scotland	-0.024 (-0.040,-0.008), p=0.005	0.031 (-0.010, 0.071), p=0.130	0.315 (-0.006, 0.635), p=0.054

Table 6.3.3. Interrupted time series regression results for trends in switching to other medications.

Country	*Before February 2015* *(per 100/quarter)*	*Change after February 2015* *(per 100/quarter)*	*Change in first quarter after February 2015* *(per 100)*
Denmark	0.066 (-0.009, 0.141), p=0.081	-0.101 (-0.237, 0.036), p=0.143	-0.471 (-1.775, 0.832), p=0.467
England	0.001 (-0.034, 0.036), p=0.933	-0.017 (-0.179, 0.145), p=0.833	0.172 (-0.818, 1.162), p=0.727
The Netherlands	0.122 (-1.539, 1.783), p=0.522	-0.355 (-3.503, 2.792), p=0.387	0.372 (-23.50,24.239), p=0.876
Scotland	-0.027 (-0.067, 0.014), p=0.192	0.095 (-0.006, 0.196), p=0.065	-0.099 (-0.909, 0.711), p=0.806

*other medications = Tricyclic antidepressants. Mirtazapine. Selective serotonin reuptake inhibitors.

7 DISCUSSION

Objective 1

Objective 1 examined the impact of the 2015 EMA regulatory intervention on hydroxyzine prescribing, initiation, discontinuation, and dose and duration of hydroxyzine-containing prescriptions within each of the four countries and by age, gender, indication and type of product. In absolute terms, the use of hydroxyzine in all countries was low suggesting it was not the preferred antihistamine being prescribed in these countries but was highest in Scotland that had around a 2-fold increased rate of hydroxyzine prescribing compared to other countries during the baseline period. The impact of the 2015 EMA regulatory intervention for hydroxyzine differed among the countries studied. The 2015 EMA regulatory intervention for hydroxyzine had a significant immediate impact and significant change in trend in the intended direction on the hydroxyzine initiation in England and Scotland but not in Denmark or in the Netherlands.

In England and Scotland, there was a positive trend in hydroxyzine exposures and prescriptions prior to the EMA regulatory intervention. For exposures there was also a negative baseline trend in initiation in the Netherlands with the regulatory intervention being associated with a significant negative trend in patients prescribed hydroxyzine in Denmark. Although the regulatory intervention was associated with significant changes in the mean daily dose of hydroxyzine prescription, in absolute terms these changes were small. It is uncertain why this may have occurred and this may have been related to the downward trend in the duration of hydroxyzine prescriptions in these countries throughout the study period.

The intervention was associated with a statistically significant rise and fall in overall hydroxyzine discontinuation in England and Denmark respectively, with no impact on hydroxyzine discontinuation in the Netherlands or Scotland. It is uncertain why there would be the pattern as observed for Denmark although it is noted that prescription duration had increased over time. However, the changes in England are more expected in that there is first an immediate increase in discontinuation with a negative trend. We believe the negative trend in this instance may be because the pool of hydroxyzine initiators is falling and most hydroxyzine exposure is one-off.

Less impact on hydroxyzine discontinuation was noted compared to initiation with significant short-term changes in the intended direction for discontinuation occurring in England only. This observation is in keeping with previous evidence that regulatory interventions tend to be more effective at decreasing initiation of targeted medicines, but less effective at bringing about their discontinuation.[12]

Objective 2

It is important to study the impact of the regulatory intervention in subgroups with particular in patients with contraindications to assess whether impact has varied between specific populations. Among the studied patients with contraindications, the regulatory intervention was associated with a significant impact on the rate of hydroxyzine initiation in patients with cardiovascular disease in England and Scotland only. In patients with concomitant exposure to drugs known to prolong the QT interval, the regulatory intervention had a significant impact in England, Scotland and also in Denmark to a less extent. No evidence was observed that the intervention was associated with a significant impact trend in hydroxyzine initiation in patients with recent electrolyte disturbance or with bradycardia. However, the number of such patients were extremely small suggesting that the population at risk is so small that evaluation of impact may lack feasibility.

Objective 3

Regulatory interventions may have unintended consequences on prescribing and health outcomes. Objective 3 set out to examine the impact of the regulatory intervention on unintended switching to other antihistamines that may have greater sedative properties than hydroxyzine, benzodiazepines that risk addiction and other antidepressant medications associated with other types of adverse effects. Reassuringly the study found that the regulatory intervention was not associated with any impact on switching to other antihistamines, benzodiazepines or other antidepressant medications following hydroxyzine discontinuation in any country. However, it is possible that changes may have occurred in medicines not examined or only with some individual products within each group.

Limitations

This study has several potential limitations. First, observed comparisons between the absolute changes in the quarterly prevalence of different products from the start to the end of the observation period may be influenced by the different lengths of follow-up for analysis between data sources.

Interrupted time series analysis was performed using different numbers of baseline time periods before the intervention that may have reduced the power to detect a significant result. The date of intervention in all countries has been pre-specified as February 2015 and the actual date of implementation may have varied. In this regard, it is possible that clinical practice may have been influenced by the evidence on the safety of hydroxyzine before the EMA referral and recommendations had been concluded. It is plausible that when baseline trends are already heading in the intended direction it may be more difficult for a regulatory intervention to have impact or for statistically significant changes to be detected. In this regard, such trends are already heading in the intended direction. Trends must therefore be interpreted clinically and not simply statistically, particularly if further regulatory action may be considered.

This study does not capture over-the-counter or non-reimbursed antihistamine exposures, the extent of which may vary by country potentially contributing to heterogeneity of results. We also do not report data on the proportion of patients continuing hydroxyzine therapy who would have been co-prescribed the same alternative medicines although this may have minimal impact on the interpretation of switching trends.

The definition for the denominators varied by data source. The denominator in the PHARMO source population are patients in the linked GP Database and the out-patient Pharmacy Database (covering 1.4 million patients). These are patients with any prescribed medication available. In contrast, in CPRD these are the population of registered patients within each general practice, whilst in Denmark these are taken from national statistics. However, expected differences are unlikely to influence changes in the trend in prescribing and interpreting the impact that the regulatory intervention may have had. There may be different coding practices between data sources that could affect how well patients with the contraindications and risk factors of interest are identified. Diagnostic codes were used as proxies for the indication of hydroxyzine and patients with multiple potential coded indications would have appeared in different indication groups more than once. However, this may reflect the close relationship between these potential indications and how the medicine is used in clinical practice. Hydroxyzine may also have been used for other conditions such as allergic rhinitis that has not been evaluated in this report.

For some patient groups, the denominators were small and hydroxyzine infrequently prescribed meaning it was not feasible to adequately fit ITS models to provide meaningful results. In this regards, due to the lack of data capture it was not possible to evaluate the impact of the regulatory intervention on hydroxyzine initiation in patients with a family history of sudden cardiac death, electrolyte disturbance or bradycardia. However, this may also be a sign that the population for whom the regulatory intervention is aimed at is reassuringly very small to begin with.

Conclusion

In conclusion, the EMA 2015 regulatory intervention targeting hydroxyzine-containing medicinal products reduced overall hydroxyzine initiation among the populations in two of the four country data sources examined. The regulatory intervention had limited impact on hydroxyzine discontinuation and no significant impact on switching suggesting limited unintended consequences may have occurred for those groups of alternative medicines examined.

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