Post-authorisation Safety Study: Risk of Out-of-Hospital Sudden Cardiac Death in Users of Domperidone, Users of Proton Pump Inhibitors, and Users of Metoclopramide

Final Protocol, Version 1.1

9 November 2012

Prepared for

Marketing Authorisation Holder: Janssen Research and Development, LLC

Daniel Fife, MD
Janssen Research and Development, LLC
1125 Trenton-Harbourton Road
PO Box 200
Titusville, NJ 08560
Telephone: +1.609.730.3419
Fax: +1.609.730.3477
E-mail: dfife@its.jnj.com

Prepared by

Alejandro Arana, MD, MPH (primary contact); Catherine Johannes, PhD

RTI Health Solutions

Trav. Gracia 56 Atico 1
08006 Barcelona, Spain
Telephone: +34.93.362.28.05
Fax: +34.93.414.26.10
E-mail: aarana@rti.org

RTI-HS Project No.: 0303209

APPROVAL PAGE

Protocol Title: Post-authorisation Safety Study: Risk of Out-of-Hospital Sudden Cardiac Death in Users of Domperidone, Users of Proton Pump Inhibitors, and Users of Metoclopramide

Protocol ID Number: RTI0303209

Authors   Alejandro Arana, MD, MPH; Catherine Johannes, PhD
(RTI Health Solutions)

Version Date: 9 November 2012

The following people have reviewed the protocol and give their approval:

RTI Health Solutions

_____   22 Nov, 2012

Alejandro Arana, MD, MPH   Signature   Date
Director, Epidemiology
RTI Health Solutions

_____   22 NOV 2012

Susana Perez-Gutthann MD, PhD   Signature   Date
Vice-President, Global Head Epidemiology
RTI Health Solutions

Funding Institution

_____   21 Nov, 2012

Daniel Fife, MD   Date
Senior Director, Epidemiology
Janssen Research and Development, L.L.C.

_____   21 Nov, 2012

Sheldon Sloan, MD, M Bioethics   Date
Internal Medicine Portfolio/Compound Development
Team Leader, Established Products
Janssen Research and Development, L.L.C.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

BMI   body mass index

CPRD   Clinical Practice Research Datalink

CYP3A4   cytochrome P450 3A4

EMA   European Medicines Agency

ENCePP   European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

GP   general practitioner

GPP   Good Pharmacoepidemiology Practices

GVP   Good Pharmacovigilance Practices

HES   Hospital Episode Statistics

ICD-10   *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*

ICH   International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ISAC   Independent Scientific Advisory Committee

ISPE   International Society for Pharmacoepidemiology

MHRA   Medicines and Healthcare products Regulatory Agency

NDD   numerical daily dose

NHS   National Health Service (UK)

ONS   Office for National Statistics (UK)

OQA   Office of Quality Assurance (RTI-HS)

OR   odds ratio

OTC   over-the-counter

PPI   proton pump inhibitor

QTc   corrected QT interval

RTI-HS   RTI Health Solutions

SAP   statistical analysis plan

SCD   sudden cardiac death

SOP   standard operating procedure

STROBE   Strengthening the Reporting of Observational Studies in Epidemiology (statement)

SVA   serious ventricular arrhythmia

UK   United Kingdom

1 TITLE

Post-authorisation Safety Study: Risk of Out-of-Hospital Sudden Cardiac Death in Users of Domperidone, Users of Proton Pump Inhibitors, and Users of Metoclopramide

2 MARKETING AUTHORISATION HOLDER

Janssen Research and Development, LLC

3 RESPONSIBLE PARTIES

RTI Health Solutions—Barcelona	**RTI Health Solutions—Waltham**
Trav. Gracia 56, Atico 1 08006 Barcelona, Spain	1440 Main Street, Suite 310 Waltham, MA 02451-1623, USA
Alejandro Arana, MD, MPH, FISPE, Director Epidemiology (primary contact)	Kenneth J. Rothman, DrPH, Distinguished Fellow, Vice President of Epidemiology Research
Cristina Varas-Lorenzo, MD, PhD, Director Epidemiology	Catherine Johannes, PhD, Director Epidemiology
Susana Perez-Gutthann, MD, PhD, Vice President, Epidemiology	

RTI Health Solutions—Research Triangle Park
3040 Cornwallis Road, PO Box 12194 RTP, NC 27709-2194, USA
Amy Ladner, MPH, Senior Research Epidemiologist

Janssen Research & Development
Address
Daniel Fife, MD, Senior Director, Epidemiology, Janssen Research and Development, L.L.C.
Sheldon Sloan, MD, M Bioethics, Internal Medicine Portfolio/Compound Development Team Leader, Established Products, Janssen Research and Development, L.L.C.

Collaborating Institutions
The Clinical Practice Research Datalink Group The Medicines and Healthcare products Regulatory Agency 5th Floor 151 Buckingham Palace Road Victoria London SW1W 9SZ England

4 ABSTRACT

Title: Post-authorisation Safety Study: Risk of Out-of-Hospital Sudden Cardiac Death in Users of Domperidone, Users of Proton Pump Inhibitors and Users of Metoclopramide, Version 1.0

Alejandro Arana, MD, MPH; Catherine Johannes, PhD; Amy Ladner; Cristina Varas-Lorenzo, MD, PhD; Kenneth J. Rothman, DrPH; Susana Perez-Gutthann, MD, PhD

Rationale and background: Domperidone is indicated for the treatment of symptoms associated with upper gastrointestinal motility disorders. A review of the available data on cardiac risks for domperidone-containing products revealed an increased risk of serious ventricular arrhythmia (SVA) or sudden cardiac death (SCD), especially in patients receiving more than 30 mg per day orally and in persons older than 60 years.

Research question and objectives: The research goal is to assess the risk of out-of-hospital SCD associated with current use of domperidone compared with the risk in periods of non-use of domperidone or use of other gastrointestinal medications. Of particular interest is the assessment of risk of SCD in relation to estimated daily dose of domperidone and to age.

Study design: This is a population-based, nested case-control study using the data from the United Kingdom's Clinical Practice Research Datalink (CPRD) for the years 2005 through 2011. An additional case-crossover analysis of SCD cases with domperidone exposure will be performed.

Population: A cohort of patients exposed to selected gastrointestinal medications will be constructed by selecting all patients with at least one prescription for domperidone, a proton pump inhibitor (PPI), or metoclopramide recorded in the database during the years 2005-2011. Institutionalised patients, patients younger than 2 years, and individuals with a diagnosis of cancer other than non-melanoma skin cancer will be excluded.

Variables: The outcome variable is out of hospital SCD. All cases of SCD occurring in the study cohort during the study time period will be identified, and the incidence of SCD will be estimated during periods of current and past exposure to each study medication and during periods of non-exposure. Domperidone is the primary exposure of interest. Comparator groups of medications are PPIs and metoclopramide.

Other medical conditions will be evaluated as comorbidities and potential confounding factors and include known risk factors for SCD (diabetes mellitus and cardiovascular disease, among others). Medications that will be evaluated for concomitant use with domperidone are corrected QT interval (QTc)–prolonging drugs and drugs that may interact with domperidone metabolism, that is, cytochrome P450 3A4 (CYP3A4) inhibitors, which can increase plasma levels of domperidone; CYP3A4-inducing drugs; and drugs that affect the protein coded by the *hErG* gene.

Data sources: In the CPRD, patients in 75% of English practices are linked individually to the Office for National Statistics (ONS) mortality data and to the Hospital Episode Statistics (HES) data, Information from both of these sources is required to establish whether deaths are due to cardiac causes and occurred in a non-institutional setting. The study source population will include only patients in these English practices.

Study size: Power calculations are based on estimates of exposure and outcome occurrence from a similar study using the databases of Saskatchewan Health. In that study, the prevalence of exposure to domperidone was 5.4%. There were 1,559 confirmed deaths from SCD in the cohort of 83,212 persons exposed to domperidone or a PPI, for an event proportion of approximately 2%. Using this proportion, the expected number of SCD cases for the current study can be estimated at 3,000, and the power to detect an odds ratio (OR) of at least 1.3 would be 85%. However, this is a rough approximation of the power, because the computation does not control for confounding or consider the effect of matching on study power.

Data analysis: The crude incidence (absolute risk) of SCD will be estimated first for the entire exposure cohort using the number of SCD events divided by the person-years of follow-up.

Incidence rates of SCD will be stratified by the following factors:

- Sex, age group, and diabetes status

- Current use of domperidone and by sex, age group, and diabetes status

- Current use of PPI medications and by sex, age group, and diabetes status

- Current use of metoclopramide and by sex, age group, and diabetes status

- Non-use of any of these medications and by sex, age group, and diabetes status

Stratified incidence rates will be calculated by dividing the number of SCD events in each relevant stratum by the number of person-years in each stratum.

Incidence rate ratios will be calculated comparing current use of domperidone with current use of PPI medications, current use of metoclopramide, and with non-use time, standardised for age and sex. For domperidone users, incidence rates will also be stratified by dose categories (< 30 mg, 30 mg, and > 30 mg), and doses higher than 30 mg/day will be further categorised into mg per day values of > 30 to ≤ 40, > 40 to ≤ 60, > 60 to ≤ 80, and > 80.

Multivariable conditional logistic regression will be used to estimate the risk of SCD from current domperidone exposure relative to the risk among those with non-use of any of the three study drug exposures (or, alternatively, to current PPI exposure and to current metoclopramide exposure), adjusted for possible confounding variables. An in-depth exploration of the dose-response trend among current domperidone users will be undertaken using the dose categories described above and by using spline regression.

A case-crossover analysis in the cases of SCD will examine the frequency of current exposure to medication at the time of SCD, as well as the frequency of current medication exposure in the control time windows while controlling for time-invariant, within-person factors. Conditional logistic regression will be performed on the matched sets. The OR with 95% confidence interval will be calculated separately for current domperidone exposure, current PPI exposure, and current metoclopramide exposure.

Milestones:

Milestone	Date
Start of data collection[a]	1 January 2013
Final report of study results	18 September 2013
Final manuscript	13 December 2013

[a] Date from which data extraction starts.

5 AMENDMENTS AND UPDATES

Not applicable.

6 MILESTONES AND TIMELINE

Table 1.   Key Study Milestones and Planned Dates of Completion

Milestone	Date
Start of data collection[a]	1 January 2013
End of data collection[b]	28 January 2013
Statistical analysis plan	04 January 2013
Draft report of study results	21 August 2013
Final report of study results	18 September 2013
Draft manuscript	15 October 2013
Final manuscript	13 December 2013

[a] Date from which data extraction starts.

[b] Date from which the analytical data set is completely available.

7 RATIONALE AND BACKGROUND

Domperidone, a peripherally acting dopamine 2–receptor antagonist with both gastrokinetic and antiemetic actions, is indicated for the treatment of symptoms associated with upper gastrointestinal motility disorders, such as diabetic gastroparesis, and with nausea and vomiting associated with therapy for Parkinson's disease and cancer (Barone, 1999; Drolet et al., 2000). Domperidone has been on the worldwide market since 1978 and is considered a therapeutic alternative to metoclopramide (Rossi and Giorgi, 2010). It is not available in the United States. It is available as both a prescription and an over-the-counter (OTC) oral medication in the United Kingdom (UK). In the UK, prescription-only domperidone is indicated in adults for "the relief of the symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents" with a maximum daily dose of 80 mg. Domperidone as a non-prescription medicine is available in pharmacies for patients aged 16 years and older for "the relief of the symptoms of nausea and vomiting" with a maximum daily dose of 40 mg (Domperidone Summary of Product Characteristics,

2011). Depending on the indication, the usual adult dose of domperidone is 10 mg or 20 mg orally taken 3 to 4 times a day, and dosing can be increased rapidly if adequate control of symptoms is not observed within a short period of time. It also may be prescribed on an "as needed" basis.

As described in a review by Rossi and Giorgi (2010), case reports and clinical studies have demonstrated prolongation of the QTc interval associated with domperidone use, and the injectable formulation was withdrawn from the market in 1986 after serious cardiac events (ventricular arrhythmia, cardiac arrest, and sudden death) were reported in cancer patients receiving high dosages of domperidone. Since then, spontaneous reporting in Canada, the UK, and the Netherlands has suggested an association of domperidone with ventricular arrhythmia, but the risk in clinical practice with the use of recommended dosages is not known (Rossi and Giorgi, 2010). In the May 2012 Drug Safety Update from the Medicines and Healthcare products Regulatory Agency (MHRA), a Europe-wide review of the available data on cardiac risks for domperidone-containing products revealed an increased risk of SVA or SCD, especially in patients receiving more than 30 mg per day orally and in persons older than 60 years (MHRA, 2012). The latest recommendations from the UK Commission on Human Medicines are to use domperidone at the lowest effective dose; avoid non-prescription domperidone use in patients with underlying cardiac disease without medical supervision; exercise caution for patients with existing abnormalities of cardiac conduction intervals, electrolyte disturbances, or underlying cardiac diseases, particularly for patients older than 60 years and receiving oral daily doses of more than 30 mg; and to avoid domperidone use with use of concomitant medications known to cause QTc prolongation (MHRA, 2012).

The main metabolic pathway of domperidone involves the CYP3A4 isoenzyme. According to the summary of product characteristics (2011), "In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone." The use of domperidone with medications that prolong the QTc interval, such as oral ketoconazole or erythromycin, could increase the risk of adverse cardiac events and is listed as a precaution for use. The Arizona Center for Education and Research on Therapeutics maintains lists of medications that can prolong the QTc interval or induce torsades de pointes (TdP) grouped as risk, possible risk, or conditional risk of TdP (http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm). Domperidone is listed among the drugs in which "Substantial evidence supports the conclusion that these drugs prolong QTc intervals and have a risk of TdP when used as directed in labeling."

Sudden cardiac death (SCD) is defined as a natural death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia. The death must be consistent with a cardiac cause (i.e., no evidence of a non-cardiac process as the underlying process responsible for the death). Sudden cardiac death could present as a witnessed sudden collapse with no pulse or respiration and death occurring within 1 hour after the onset of cardiovascular symptoms, or an unwitnessed death in a person known to be alive and in a stable medical condition in the 24 hours before the death was reported (Chung et al., 2010; Ray et al., 2001; Ray et al., 2004; Ray et al., 2009; Straus et al., 2005). Sudden cardiac death occurs most frequently in patients with cardiac structural abnormalities or electrophysiological abnormalities (Huikuri et al., 2001). Sudden cardiac death most frequently results from the onset of acute ventricular tachyarrhythmias triggered by acute myocardial ischaemia in an individual with or without known ischaemic heart disease In addition to myocardial ischaemia, other triggering mechanisms include

systemic metabolic and hemodynamic alterations, neurochemical or neurophysiological factors, and exogenous toxic or pharmacological effects.

Population-based case-control studies in the Integrated Primary Care Information database in the Netherlands have found an increased risk of SCD or a combined outcome of SCD and SVA with current use of domperidone compared with non-use (Straus et al., 2005; van Noord et al., 2010). Both studies were based on very few domperidone-exposed cases and controls. The study by Straus and colleagues was designed to look at non-cardiac QTc-prolonging drugs as a class, not domperidone alone, and found a 4-fold increase in the odds of SCD among current domperidone users compared with non-use of non-cardiac QTc-prolonging medications (Straus et al., 2005). A nested case-control study in the Canadian Saskatchewan databases found that current domperidone use was associated with a 44% increase in the risk of SVA/SCD compared with current use of PPIs, and a 59% increase compared with non-use of either type of medication (Johannes et al., 2010). The more recent study in the Netherlands Integrated Primary Care Information database by van Noord and colleagues found a 2-fold increase in the risk of SVA/SCD as a combined outcome in fully adjusted analyses of current domperidone use compared with never use (van Noord et al., 2010). Of the three aforementioned studies, only the study by van Noord and colleagues (2010) included an analysis of domperidone dosage and SCD risk, and found an 11-fold increase in the risk of SVA/SCD associated with daily doses greater than 30 mg. However, the number of cases (n = 4) and controls (n = 3) exposed to this dosage was small.

The current study will contribute additional information by providing an in-depth analysis of the dose-response trends of current domperidone exposure on the risk of SCD, evaluating metoclopramide use as a comparator medication in addition to PPIs, and including a case-crossover analysis to evaluate the possible impact of residual confounding by indication on risk estimates.

8 RESEARCH QUESTION AND OBJECTIVES

The overall research goal is to assess the risk of out-of-hospital SCD associated with current use of domperidone compared with the risk in periods of non-use of domperidone or use of other specific gastrointestinal medications. Of particular interest is the assessment of risk of SCD in relation to estimated daily dose of domperidone and to age.

The research objectives are as follows:

- Estimate the absolute risk of out-of-hospital SCD associated with exposure to domperidone, exposure to PPI medications, exposure to metoclopramide, and periods of non-exposure to such medications.

- Estimate the risk of out-of-hospital SCD during current domperidone use relative to risk during current PPI use, to risk during current metoclopramide use, and to risk during periods of non-use of any of the medications, adjusted for demographic characteristics, medical conditions, medications, and other potentially confounding factors.

- Examine the relation of risk of out-of-hospital SCD by age and estimated daily dose of domperidone for current use of domperidone.

- ▪ Among cases of SCD, compare the domperidone exposure frequency at the date of SCD with the exposure frequency during control windows of time before the occurrence of SCD. Conduct similar comparisons for exposure to PPI medications and to metoclopramide (case-crossover analyses to explore residual confounding).

The research objectives will be addressed by conducting a population-based case-control study nested in a cohort of patients with at least one recorded prescription for domperidone, any PPI medication, or metoclopramide from 2005-2011. Patients must have at least 1 year of continuous enrollment in an up-to-standard[1] English practice before cohort entry. The study outcome will be evaluated by linking the general practice data to HES data and to death certificates collected by the ONS. The comparison of domperidone exposure with other gastrointestinal medications (PPI and metoclopramide) will reduce the possibility of confounding by indication that could occur when comparing users of a gastrointestinal medication with non-users. To date, there is insufficient published evidence to suggest an association of the PPIs or metoclopramide with SCD. To further avoid the possibility of confounding, a case-crossover analysis in the cases of SCD, to examine the risk during periods of use compared with the risk during periods of non-use for the same individuals, will be performed. Estimates from this analysis will also be stratified on daily domperidone dose categories and by age group categories.

9 RESEARCH METHODS

9.1 Study Design

This is a population-based, nested case-control study using the data from a single database in the UK, the CPRD, for the years 2005 through 2011. During these years, CPRD patients in 75% of English practices are linked individually to the ONS and to HES data, England's national statistical data warehouse for care provided by National Health Service (NHS) hospitals. Information from both of these sources is required to establish whether deaths were due to cardiac causes and occurred in a non-institutional setting. Currently, these linkages can be performed only with data from certain English practices and for periods when linkage is available; therefore, the study cohort will include only patients in these English practices and person-time that ensures availability of the information. A cohort of patients exposed to gastrointestinal medications will be constructed by selecting all patients with at least one prescription for domperidone, a PPI medication, or metoclopramide recorded in the database during the study period. Individuals with a previous diagnosis of cancer other than non-melanoma skin cancer will be excluded. All cases of out-of-hospital SCD occurring in the exposure cohort during the study time period will be identified, and the incidence of SCD will be estimated during periods of exposure to each study medication and during periods of non-exposure.

Entry into the exposure cohort will occur on the date of the first recorded drug prescription after 1 year of continuous registration in the CPRD before cohort entry, and person-time will continue until the earliest of date of last practice data collection, transfer out from the practice, diagnosis of cancer other than non-melanoma skin

---

[1] Up-to-standard practices meet minimum requirements for research-quality data.

cancer, death, or the study end date. Cases of SCD occurring during the observation period of the exposure cohort will be ascertained and all person-time in the exposure cohort will be classified into periods of current use, past use, and non-use of domperidone, PPIs, and metoclopramide. The comparison of domperidone to users of other gastrointestinal medications (PPIs or metoclopramide) is designed to reduce confounding by indication. Because of the intermittent use of these medications, the rates of SCD will be measured during periods of current use, as well as during periods of non-exposure to any of these medications.

The study will include two different analytic approaches to control for confounding: (1) a nested case-control approach comparing SCD cases with matched controls, matching on potential strong confounding variables and adjusting for other variables in multivariate models, and (2) a case-crossover analysis in the cases of SCD to examine the risk during periods of use compared with the risk during periods of non-use. A specific focus of the study will be estimation of the daily dose of domperidone to explore the possible dose-response relationship of domperidone use to SCD risk in current domperidone users.

Analyses will include descriptive analyses, calculation of incidence of SCD by exposure categories in the entire exposure cohort, evaluation of possible confounding variables, multivariable conditional logistic regression, and sensitivity analyses. In addition, for domperidone exposure, we will fit a smoothed dose-response trend line.

As a sensitivity analysis, an additional case-crossover analysis of SCD cases with domperidone exposure will be performed to compare exposure at the time of the occurrence of SCD with control time windows randomly selected from the at-risk person-time of each individual. This type of self-matching design eliminates between-person confounding by time-invariant characteristics, including chronic medical conditions, and may partially control for time-varying factors (Maclure, 1991; Schneeweiss et al., 1997).

9.1.1 Study Tasks

Key project tasks are as follows:

- Task 1: Develop statistical analysis plan (SAP) and prepare query specifications for CPRD data extraction
- Task 2: Acquire access to data and conduct analyses
- Task 3: Conduct physician survey on domperidone dosage
- Task 4: Prepare study report
- Task 5: Produce abstract and manuscript
- Task 6: Manage project coordination and communication

9.2 Setting

The base population is derived from the CPRD, a primary care database containing longitudinal data from anonymised electronic medical records of patients from general practitioners (GPs) in the UK who provide primary health care and specialist referrals. The database contains data for about 6% of the population of the UK (Herrett et al., 2010). The study population will be selected from all individuals registered in English

practices whose data are linkable to HES and ONS data and included in the CPRD for at least 1 continuous year. Patients will join the cohort at their first exposure to a study drug (domperidone, PPI, or metoclopramide) after at least 1 continuous year of enrolment in the CPRD. Only patients with permanent registration status in up-to-standard practices will be included.

The following exclusion criteria will be applied to obtain the study cohort:

- Individuals with a diagnosis of cancer other than non-melanoma skin cancer will be excluded. The study outcome is unexpected, sudden death from cardiac causes, and death in persons with cancer is often difficult to assess, is usually expected, and is unlikely to be of cardiac origin. In addition, one of the indications for domperidone use is nausea and vomiting related to cancer chemotherapy, and some chemotherapy drugs are associated with life-threatening cardiotoxic side effects. All members of the exposure cohort with a diagnosis of cancer during the baseline period will be excluded from analyses. This exclusion will be made without regard to case, control, or exposure status. Person-time of individuals will be truncated if a diagnosis of cancer occurs during follow-up.

- Patients from practices not linkable to HES and ONS data will be excluded. Linkage to the HES to obtain hospital information and to the Office of National Statistics (ONS) to obtain information from death certificates on date and cause of death is necessary for ascertaining and verifying the study outcome. Among patients from practices linkable to HES and ONS, only the person-time linkable to HES and ONS will be considered.

- Individuals younger than 2 years will be excluded because of the difficulty to assess sudden infant death and because there is no liquid preparation of oral domperidone available. Thus, it would be unlikely for oral exposure to domperidone to occur in this age group.

- Patients residing in institutions (Read codes 13F5. 13F72, 13FK, 13FT, 13FV, 13FX) will be excluded because many deaths in this setting are not unexpected and little or no investigation of deaths in this setting occurs.

- Person time corresponding to the period between admission date and 30 days after discharge date will be excluded to ensure time at risk occurs outside a hospital setting using information on admission and discharge dates from HES data.

9.2.1 Follow-up of Subjects

- Follow-up will continue until the earliest date of diagnosis of a cancer other than non-melanoma skin cancer, date of transfer out from a practice, date of death, or study end date.

9.3 Variables

9.3.1 Exposures

Domperidone is the primary exposure of interest, and the two comparator groups of medications are PPIs and metoclopramide. Individual PPI medications will be grouped

into one category for analyses. PPI medications available in the UK are omeprazole (Losec), lansoprazole (Zoton), esomeprazole (Nexium), pantoprazole (Protium), and rabeprazole (Pariet). Of these, omeprazole is available as an OTC medication in the UK.

The exposure cohort will be defined by prescriptions of domperidone, a PPI medication, or metoclopramide, as follows:

- Subjects enter the study with the first recorded prescription for domperidone, a PPI, or metoclopramide between January 1, 2005, and December 31, 2011.

- All subjects have at least 1 year of continuous registration in an eligible English practice.

- Subjects must be aged at least 2 years upon cohort entry.

- *Cohort entry date* is the date of the first domperidone, PPI, or metoclopramide prescription that qualifies the subject for study inclusion.

- *Study exit date* is the earliest of date of last data collection at the practice, date of diagnosis of a cancer other than non-melanoma skin cancer, date of death, or December 31, 2011.

Variables available for exposure assessment in the CPRD include prescription date, total quantity prescribed, number of packs, and the prescription duration. Using this prescribing information, mutually exclusive intervals of continuous current exposure to each drug over the entire person-time of each individual will be created by adding the duration of each consecutive prescription plus 7 days to account for carry-over effects as in prior research (van Noord et al., 2010). Person-time outside these intervals will be considered past use or non-use time. The occurrence of concomitant exposure to domperidone and either or both of the two comparison medications will also be recorded and categorised as necessary for analyses. Routes of administration of the medications other than oral will be classified into a separate exposure category for the period corresponding to the duration of use plus 7 days.

Exposure to each type of study drug will be evaluated separately, and exposure time will be categorised as current use, past use, and non-use for the entire follow-up time of each cohort member, beginning with the first recorded prescription on the cohort entry date. The mutually exclusive exposure categories are defined as follows:

- *Current use:* Time from date of prescription to end of calculated duration of exposure (duration of prescription plus 7 days).

- *Past use:* The 60 days after the end of the current use time-window.

- *Non-use:* Study person-time outside of current use or past use windows.

The rate of out-of-hospital SCD will be calculated during periods of current and past exposure to domperidone, PPI, or metoclopramide and during periods of non-use of any of the three drugs (Figure 1).

Figure 1. Diagram of Exposure Category Definitions

9.3.1.1 Estimation of Daily Dose of Domperidone

All available data will be used to estimate the daily dose for domperidone. The CPRD prescription records contain numerical information on the total quantity prescribed, the number of packs, and the prescription duration. However, of these, only the quantity variable is populated most of the time. Dosing instructions to the patient are contained in the free-text notes and not provided as numerical values in the database.

A computerised algorithm has been created to derive a numerical daily dose (NDD) from dosage instructions in the CPRD free text (Shah and Martinez, 2006). Derived NDD values recorded in the CPRD are populated using this algorithm. From preliminary analyses performed prior to study initiation, it was determined that approximately 73% of domperidone prescriptions in the CPRD on or after January 1, 2005, have a derived NDD value recorded.

The NDD does not reflect "as needed" instructions, which are common for domperidone. For those prescriptions without a derived NDD value available, the following steps will be taken:

- Conduct a physician survey to obtain missing dose information for all cases and controls with current exposure to domperidone at the index date

- If the physician survey does not yield the dose information, estimate dose by multiple imputation; the proportion of cases and controls with dose estimated by multiple imputation will be clearly specified in the study report

Note that the physician survey will also be conducted to confirm information on dosage of domperidone in a small sample of patients with NDD information available. For the physician survey, a brief questionnaire regarding the prescription information will be developed and delivered to each physician to obtain information on the dosage prescribed to the patient at the point in time corresponding to the SCD death date or the corresponding index date for the control. The questionnaire for cases will be more extensive to obtain dosage information on each relevant exposure window for the case-crossover analysis.

Planned daily dose categories of domperidone for analyses are < 30 mg, 30 mg, and > 30 mg. We will also investigate the dose relationship for daily doses of domperidone > 30 mg categorised into mg per day values of > 30 to ≤ 40, > 40 to ≤ 60, > 60 to ≤ 80 and > 80.

9.3.1.2 Estimation of Duration of Domperidone Exposure

The CPRD prescription records contain numerical information on the prescription duration. However, this variable is not populated most of the time. The following steps will be taken for individuals with missing information on duration of exposure:

- Conduct a physician survey in a sample of the population to obtain missing information on the duration of domperidone prescriptions

- If the information for a particular exposure episode is still missing and the individual has more than one prescription of domperidone, estimate duration based on the intervals between domperidone prescriptions for that subject

- If there is only one prescription for an individual, calculate duration of use by halving the average length of time between the first and second prescription for those individuals with a first and second prescription

9.3.1.3 Evaluation of Seasonal Trends on Domperidone Prescribing

The proportion of domperidone-exposed days by month during the study period will be determined, and seasonal trends will be examined using periodic regression, as implemented on Episheet (Rothman, 2011).

9.3.1.4 Evaluation of Indication for Domperidone

Indication is not recorded in the CPRD except for new prescriptions. Because there are several different indications for domperidone, it would be preferable to conduct analyses stratified by domperidone indication. To be used as proxies of indication, subjects with medical diagnoses of diabetes and motility disorders recorded in the database during the month prior to the date of prescription for domperidone will be identified. Analyses will be performed separately for these subjects. We will use the physician questionnaire to determine the indication in a sample of patients

9.3.2 Outcome

The study endpoint is SCD occurring out of the hospital. Sudden cardiac death is defined as a natural death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia. The death must be consistent with a cardiac cause (i.e., no evidence of a non-cardiac underlying process responsible for the death). Sudden cardiac death could present as a witnessed sudden collapse with no pulse or respiration and death occurring within 1 hour after the onset of cardiovascular symptoms, or an unwitnessed death in a person known to be alive and in a stable medical condition in the 24 hours before the death was reported (Chung et al., 2010; Ray et al., 2001; Ray et al., 2004; Ray et al., 2009; Straus et al., 2005).

All deaths occurring during the person-time of the exposure cohort will be identified without regard to study drug exposure status by linking the CPRD electronic data with the Office of National Statistic's (ONS) death certificate information, which includes the date and causes of death, coded using *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes. Researchers from the CPRD have found that death rates by age group (except for ages < 1 year) and various causes of death, including ischaemic heart disease, are comparable between linked CPRD data and official rates for England and Wales (Setakis et al., 2010). The authors reported that, overall, the subset of linked CPRD practices is a representative sample of the general population (Setakis et al., 2010).

A published validated computer case definition for out-of-hospital SCD will be applied for this study (Chung et al., 2010).

1. Using information recorded in the ONS mortality data, deaths occurring during the follow-up with an underlying cause of death with an ICD-10 diagnosis code listed in Table 2 will be identified. These codes have been reported with a high positive predictive value for SCD (Ray et al., 2009; Chung et al., 2010).

2. The deaths identified in step 1 will then be evaluated for their occurrence outside a hospital setting. Linked ONS mortality data and Hospital Episode Statistic (HES) activity permits identification of deaths that occur outside hospitals. The ONS mortality data contain date of death, place of death, and multiple recorded causes of death, including the underlying cause of death, which takes into account additional information provided by medical practitioners or coroners after the death has been registered. The HES includes activity information on admitted patient care or inpatient, outpatient, and accident or emergency attendances. All deaths with recorded date of death outside the period of time between dates of hospital episodes defined by admission and discharge dates plus 30 days will be identified. We will retain as final cases of SCD only those cardiac deaths with an underlying cause of death diagnosis code consistent with SCD and without alternative non-cardiac cause of death that occur in a non-institutional setting. We will also include sudden cardiac arrests that occurred outside the hospital but were attended in an emergency room setting and the death occurred while in the emergency room, unless there are terminal procedures present that are inconsistent with unresuscitated cardiac arrest (Chung et al., 2010).

3. The *case index date* will be the date of SCD as verified by linkage with the death certificate information.

Table 2.   ICD-10 Codes for Underlying Cause of Death for Computer Identification of Out-of-Hospital Sudden Cardiac Death (Reported to be Highly Predictive of Sudden Cardiac Death)

ICD-10 Code	Description
I10	Essential (primary) hypertension
I11.9	Hypertensive heart disease without heart failure
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications of acute myocardial infarction
I24	Other acute ischaemic heart disease
I25	Chronic ischaemic heart disease
I25.2	Old myocardial infarction
I20	Angina pectoris
I42.8,I42.9	Cardiomyopathy, NOS
I46	Cardiac arrest
I47.0	Re-entry ventricular arrhythmia
I47.2	Ventricular tachycardia
I49.0	Ventricular fibrillation and flutter
I49.8	Other specified arrhythmias
I49.9	Cardiac arrhythmia, unspecified
I51.9	Heart disease, unspecified
I51.6	Cardiovascular disease, unspecified
I70.9	Atherosclerosis, NOS
R96.1	Death < 24 hours after symptoms
R98	Unattended death

ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; NOS = not otherwise specified.

Source: Chung et al 2010; Ray et al., 2009.

9.3.3 Other Variables

The selection of variables to be evaluated as potential confounding variables is based on known risk factors for SCD and factors associated with prescribing of domperidone identified from review of the literature and from previous work. The confounding variables of interest include medical conditions, medications, indicators of health care utilisation, and lifestyle variables as described below. Additional variables that may be added post hoc will be clearly identified as such.

9.3.3.1 Medical Conditions

The following medical conditions will be evaluated as comorbidities and potential confounding factors and include known risk factors for SCD; they will be identified by diagnoses provided by the GP and specialists as recorded in the electronic medical

records. Most conditions will be evaluated as of the date of cohort entry (i.e., history of the condition before cohort entry) and, among individuals without the condition at cohort entry, during the follow-up time. Acute events, such as stroke, myocardial infarction, and hospitalisation for heart failure, are associated with an elevated risk of SCD in the first 3 months after occurrence. Sudden cardiac death occurring in patients with one of these events within 30 days will be attributed to the event. We will create indicator variables for cardiovascular deaths that occurred 31 to 90 days after one of these acute medical conditions. These indicator variables will be used to perform sensitivity analyses to examine effect estimates with these deaths included or excluded.

- Diabetes mellitus (3-level variable)
  - Diabetes mellitus with diagnosis code
  - Diabetes mellitus diagnosis code with evidence of poor glycemia control. Hemoglobin A1c > 6.5% in the 6 months before index date
  - Severe diabetes mellitus – diagnosis code with one of the following: insulin prescription or a diagnosis code for diabetic neuropathy, nephropathy, or retinopathy; lower limb ulcers; or amputations in the year before the index date
- History of ventricular tachycardia/ventricular fibrillation and flutter at cohort entry
- Other domperidone indication
  - Gastroparesis
  - Diabetic gastroparesis
- Autonomic neuropathy
- Cerebrovascular disease (history at cohort entry and new occurrence during the follow-up time)
- Cardiovascular disease (history at cohort entry for history of condition and new occurrence during the follow-up time)
  - Ischaemic heart disease (myocardial infarction, acute coronary syndrome, coronary revascularisation procedure)
  - Heart failure
  - Pulmonary heart disease
  - Valvular heart disease, including valve replacement
  - Cardiomyopathies
  - Other arrhythmias (not ventricular tachycardia/ventricular fibrillation and flutter) or conduction disorders
  - Electrophysiology procedures for treatment of arrhythmias
- Renal impairment, including end-stage renal disease and dialysis
- Hypertension
- Hypercholesterolemia
- Severe chronic obstructive pulmonary disease (oxygen therapy, oral corticosteroids, presence of pulmonary emphysema)

- Asthma

- Epilepsy

- Depression

- Schizophrenia

- Gastrointestinal conditions:

  – Dyspepsia

  – Gastric or peptic ulcer

  – Gastritis and duodenitis

  – Gastroesophageal reflux disease

  – Disorders of stomach/duodenum

  – Symptoms involving digestive system

  – Liver failure

  – Hepatic impairment

9.3.3.2 Medications

Variables that will be evaluated for concomitant use with domperidone are QTc-prolonging and drugs that may interact with domperidone metabolism. Use of the following medications will be categorised as current use, past use, or non-use *at the index date* in a manner similar to the process for defining exposure to domperidone, PPIs, and metoclopramide:

- QTc-prolonging drugs that may cause arrhythmia or prolong the QTc interval will be assessed from the most recent lists available from the Arizona Center for Research on Therapeutics Web site (http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm). Separate variables will be created for each of the two groups of QTc-prolonging drugs:

  – Group 1 (drugs with a risk of torsades de pointes)

  – Group 2 (drugs with a possible risk of torsades de pointes)

- CYP3A4 inhibitors (drugs that can increase plasma levels of domperidone with concomitant use). These drugs will be grouped for analysis into two separate variables: strong and weak CYP3A4 inhibitors.

- Other drugs that may interact with domperidone metabolism will also be included as separate variables. These are listed as follows:

  – CYP3A4-inducing drugs

  – Drugs that affect the *hErG* gene

  – Digoxin

  – Diuretics

  – Laxatives

  – Systemic β-adrenergic receptor agonists

  – Oral corticosteroids

The below categories of medications will be evaluated as covariates and possible confounders of the association between domperidone and SCD and, as such, will be assessed as use or non-use during the 365 days before the index date.

For the following medications, one dichotomous variable will be created for each medication category with all medications in that category grouped into the variable. The variable will be categorised as use if at least one prescription is present in the 365 days before the index date and no use if no prescriptions are present during this time period.

- Gastrointestinal medications other than domperidone, PPI, or metoclopramide; this variable includes H2 antagonists and other gastrointestinal agents combined

- Antihypertensive medications

  - Angiotensin-converting enzyme inhibitors

  - Angiotensin receptor blockers

  - Alpha-adrenergic agonist/blocker

  - Other antihypertensive agents

- Antiarrhythmic agents with action on repolarisation time (class I and III antiarrhythmics such as propafenone, sotalol, tocainide, disopyramide, procainamide, quinidine, mexiletine, flecainide, and amiodarone)

- Antiarrhythmic agents without action on repolarisation (class IV antiarrhythmics such as verapamil and diltiazem)

- Beta blockers

- Other cardiac medications (including lipid-lowering agents, chronic heart failure agents other than digitalis, nitrates, calcium channel blockers, and prescription aspirin for prevention of cardiovascular disease)

9.3.3.3 Other Covariates

- Health care utilisation, defined as the number of GP visits and number of hospital episodes in the in year before the index date. These variables will be used as a continuous variable or categorised in analyses depending on the distribution.

- Amount of time in the cohort before the index date (continuous variable).

- Lifestyle variables: data on height and weight (for calculation of body mass index [BMI], or recorded BMI value), smoking history, and alcohol use are recorded for approximately 70% of patients in the CPRD. In addition, the availability of recorded information on drug abuse will also be explored. The extent of missing information for these variables will be determined before using them in analyses. If there is substantial missing information for one or more important covariates, we will consider implementing multiple imputation to address the missing data. Body mass index will be categorised for analyses (in kg/m^2) as < 18.5, 18.5-24.9, 25.0-29.9, and ≥ 30. Cigarette smoking will be categorised as current, former, and never.

9.4 Data Sources

The data source for the current study is the UK CPRD, a primary health care electronic medical record database. According to the CPRD Web site (http://www.cprd.com/intro.asp), the CPRD is the new English NHS observational data and interventional research service, jointly funded by the NHS National Institute for Health Research and MHRA. The CPRD was developed from the General Practice Research Database (GPRD) with knowledge gained from the Research Capability Programme. The CPRD took over all the GPRD and Research Capability Programme activities as of April 2012.

The CPRD contains longitudinal data from the electronic medical records of patients of GPs in the UK who provide primary health care and specialist referrals. The CPRD covers approximately 6% of the UK population and is representative of the general UK population (Herrett et al., 2010). There are just over 13 million patients in total in the database, with approximately 5.2 million active patients (valid registration data and currently registered with a GP) as of the October 2011 database build, with continuous follow-up for at least 6 years in most practices. Data recorded in the CPRD include demographic information (age and sex), medical diagnoses that are part of routine clinical care or clinical events including the date and location of the event, details of all outpatient prescriptions, preventive care, specialist referrals and specialty consultation notes, and hospital admissions and their major outcomes (Gelfand et al., 2005). Medical diagnoses are classified using Read codes. Prescription information includes the date of the prescription, formulation, strength, quantity, route of administration, dosing instructions, and indications for treatment (for new treatments). The CPRD prescription records contain numerical information on the total quantity prescribed, the number of packs, and the prescription duration; however, of these, only the quantity variable is populated most of the time. Dosing instructions to the patient are contained in free-text notes.

Strengths of the CPRD for observational research include the size of the database, the recording of a virtually complete medical history of patients, and the representativeness of patient and practice characteristics (Herrett et al., 2010). The validity of information in the CPRD has been studied extensively, and data generated from the GP is generally complete, but about 10% of the time, data from specialists and hospitalisations may be missing. In addition, data on body weight and height, smoking, and alcohol use are available on only about 70% of patients (Gelfand et al., 2005). Except for prescriptions from secondary care and for OTC medications, which are not included in the database, the prescription data in the CPRD is very complete, as prescriptions are computer-generated by the GP and are automatically recorded in the database (Gelfand et al., 2005; Herrett et al., 2010). A service of the CPRD allows surveys to be sent to GPs about individual patients when additional information is needed. Personally identifying information from such surveys is redacted before data are sent to the researcher.

Data for the years 2005-2011 will be included in the proposed study. During these years, CPRD data for patients in 75% of English practices are linked individually and anonymously to the HES, England's national statistical data warehouse for care provided by NHS hospitals, and to death certificates collected by the ONS, which record the date and cause of death using ICD-10 codes (Gallagher et al., 2011; Van Staa et al., 2011). These linkages represent about 50% of patients in the CPRD from all regions in the UK. Linkage to this information will be necessary for the current study to document out-of-

hospital SCD. Because these linkages are available for only 75% of English practices in the CPRD, the study will be performed using only data from English practices with the linkages. To determine whether the patient population from the 25% of practices without linkages is similar to that from the 75% of practices with linkages, a descriptive analysis will be performed to compare characteristics of patients from linked and unlinked practices.

9.5   Study Size

Power calculations are based on estimates of exposure and outcome occurrence from a similar study using the databases of Saskatchewan Health. In that study, the prevalence of exposure to domperidone in the Saskatchewan database was 5.4%. There were 1,559 confirmed deaths from SCD in the cohort of 83,212 persons exposed to domperidone or a PPI, for an event proportion of approximately 2%.

Case-control power calculations were performed using Episheet (Rothman, 2011) for various values of the OR and different estimates of the number of confirmed cases of SCD using the following assumptions: exposure prevalence of 0.05, Z-alpha = 1.96, and 4 controls per case (Table 3). Preliminary calculations using CPRD data indicated approximately 160,000 persons with at least one prescription for domperidone from January 1, 2005, through the end of January 2012. Using the percentage of the exposure cohort who experienced SCD from the Saskatchewan study yields an estimate of 3,000 cases.

With 3,000 cases, the power to detect an OR of at least 1.3 would be 85%. Therefore, sufficient power is expected in the current study to detect ORs of the range (1.5 to 4.0) reported in previous observational studies of domperidone use and SCD and SVA from the Netherlands and the United States (Johannes et al., 2010; Straus et al., 2005; van Noord et al., 2010). However, this computation provides a only rough approximation of the power because it does not control for confounding, nor does it consider the matching, in which loss of concordant matched case-control sets would reduce power. Because we are using four controls for each case, the probability of finding the entire set belonging to the same category of exposure is low. Therefore, it is unlikely that a substantial loss of power would occur because of concordant case-control sets.

Table 3.   Case-Control Power to Detect Different Values of the Odds Ratio for Different Estimates of the Number of SCD Cases

Estimated Number of SCD Cases	Case-Control Odds Ratio						
	1.2	1.3	1.4	1.5	2	2.5	3
500	0.144	0.254	0.388	0.528	0.948	0.998	0.999
1,000	0.234	0.431	0.636	0.799	0.999	0.999	1.000
1,500	0.320	0.580	0.798	0.923	0.999	1.000	1.000
2,000	0.401	0.697	0.892	0.973	0.999	1.000	1.000
2,500	0.476	0.786	0.945	0.991	1.000	1.000	1.000
3,000	0.545	0.852	0.973	0.998	1.000	1.000	1.000

SCD = sudden cardiac death.

9.6   Data Collection and Management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programmes. The CPRD will maintain any patient-identifying information securely on site according to internal standard operating procedures (SOPs).

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with periodic backup of files to tape. Standard procedures will be in place to restore files in the event of a hardware or software failure.

9.7   Data Analysis

Data analysis will be performed by experienced epidemiological and statistical analysts at RTI Health Solutions (RTI-HS) according to an SAP. The SAP will serve as a roadmap to identify the patient population of interest and the subsequent analyses that are to take place. Analyses will be performed using the statistical software SAS® for Windows and SAS for Linux (version 9.2 or higher) (SAS Institute, Inc., Cary, North Carolina). To ensure the integrity and quality of the study results, a programming validation life cycle process is followed for all analyses that includes quality checking programmes, logs, and output for accuracy according to relevant SOPs.

The plan will address topics including, but not limited to, the following:

- Analysis goals and outcome measure

- Construction of the study cohort of exposed patients

- Development of analysis data sets

- Key inclusion and exclusion criteria

- Selection of controls and matching criteria

- Variables and definitions necessary for the analysis

The SAP will outline in detail the following:

- Methods for the following proposed statistical analysis:

  - Descriptive analyses of demographic characteristics and comorbidities of the study cohort (frequency and percentage estimates will be computed for categorical variables, and mean and variance values will be computed for continuous variables)

  - Calculation of incidence of SCD and planned stratifications

  - Calculation of relative risk of SCD (domperidone-exposed person-time compared with PPI-exposed person-time, metoclopramide-exposed person-time, and person-time with no exposure to domperidone, PPIs, or metoclopramide)

  - Calculation of daily dose of domperidone and incorporation of physician survey results

- Conduct of nested case-control analysis, including unadjusted analyses, evaluation of variables for confounding, multivariable models for adjusted analyses, and planned stratifications

- Analysis of dose-response effect of domperidone use on risk of SCD

- Evaluation of duration of use of domperidone

- Case-crossover analysis

▪ Handling of missing data

▪ Table shells for presenting results

Analyses will include descriptive analyses, estimation of absolute and relative risk, evaluation of possible confounding variables, multivariable conditional logistic regression, and sensitivity analyses.

9.7.1 Estimation of Absolute and Relative Risk

Cases of SCD occurring during the observation period in the entire exposure cohort will be ascertained independent of exposure history. All person-time in the exposure cohort will be classified into periods of current use and non-use of domperidone, PPIs, and metoclopramide. All individual PPI medications will be grouped into one category for analyses.

The overall crude incidence (absolute risk) of SCD will be estimated first for the entire exposure cohort using the number of SCD events divided by the person-years of follow-up.

Incidence rates of SCD will be stratified by:

▪ Sex, age group in years (2-15; 16-25; 26-35; 36-45; 46-55; 56-65; 66-75; 76-85; > 85), and diabetes status

▪ Current use of domperidone and by sex, age group, and diabetes status

▪ Current use of PPI medications and by sex, age group, and diabetes status

▪ Current use of metoclopramide and by sex, age group, and diabetes status

▪ Non-use of any of these medications and by sex, age group, and diabetes status

Stratified incidence rates will be calculated by dividing the number of SCD events in each relevant stratum by the number of person-years in each stratum.

Incidence rate ratios and risk differences will be calculated comparing current use of domperidone with current use of PPI medications, current use of metoclopramide, and with non-use time, standardised for sex and age group. For domperidone users, incidence rates will also be stratified by dose categories in mg per day (< 30, 30, > 30 to ≤ 40, > 40 to ≤ 60, > 60 to ≤ 80 and > 80).

9.7.2 Nested Case-Control Analysis

The goals of the nested case-control analyses will be to evaluate the risk of out-of-hospital SCD during current use of domperidone, PPIs, or metoclopramide relative to non-use of any of these medications and, alternatively, during current use of

domperidone relative to current use of PPIs and relative to current use of metoclopramide. The case index date will be the date of death for cases of SCD.

9.7.2.1 Control Selection and Matching

Controls will be selected using risk set sampling randomly from the person-time of all cohort members at risk of an event on the case index date. Four eligible controls will be matched to each case by case index date, year of birth, sex, and practice, as follows:

- A risk set will be created for each case, selected from the potential control person-time, in subjects with the following attributes (note that a given subject can appear in more than one risk set if the inclusion/exclusion criteria for selecting matched controls were the same for multiple cases):

  - Potential control is at risk of experiencing the study outcome and was enrolled in the practice on the index date of the case—i.e., case's index date falls within the date range of the potential control's cohort entry date to the potential control's exit/death date (both inclusive).

  - Potential control is in the same practice as the case.

  - Potential control has the same year of birth as the case.

  - Potential control is of the same sex as the case.

9.7.2.2 Evaluation of Possible Confounding Factors

Covariate status for unmatched factors and study drug exposure at the index date will be evaluated among cases and controls based on prescription and diagnostic information during the year before the index date. Exposure to each of the study medications will be considered current if the index date falls within the calculated duration of exposure. Person-time that falls outside the calculated duration of exposure will be considered past use (60 days after the end of current use) or non-use person-time.

To assess the relation of possible confounding factors to exposure in the selected control population, frequency tables will be constructed to examine the distribution of demographic variables (age at cohort entry, sex), year of cohort entry, practice, and the possible confounding variables listed by current exposure to domperidone, PPI, or metoclopramide at the index date of the selected controls.

9.7.2.3 Unadjusted Analyses

To evaluate whether exposure to domperidone alone is related to the outcome of SCD, conditional logistic regression will be used to model current domperidone use unadjusted for any covariates other than the matching variables against the outcome of SCD (conditional on the matching variables). Separate models will use different reference categories for current domperidone exposure—(1) non-use of either comparator drug class, (2) current PPI use, and (3) current metoclopramide use—to calculate ORs with 95% confidence intervals as estimates of relative risk.

9.7.2.4 Multivariable (Adjusted Analyses)

First, individual conditional logistic regression models for each covariate along with the exposure variable (current domperidone exposure using non-use as the reference category) will be constructed with SCD as the outcome. The effect (if any) of each individual covariate on the effect estimate (OR) of current domperidone use compared

with non-use on the outcome will be measured. A change in estimation procedure will be used to determine whether the covariate changed the value of the OR by at least 5%. Results of the individual regression models indicating the strength of the associations between the covariates and SCD, the distributions of the covariates in the selected control population, and information from published literature on important risk factors for SCD will be used to select variables for inclusion in the multivariable models. Multivariable conditional logistic regression will be used to estimate the odds of current domperidone exposure relative to non-use of any of the three study drug exposures (or, alternatively, to current PPI exposure and to current metoclopramide exposure), adjusted for possible confounding variables. In addition, the models will include a variable to indicate past exposure to domperidone relative to non-use of any of the three study drug exposures. The absence of an association of past use with increased risk of SCD would provide evidence against substantial confounding by indication.

If the problem of over-fitting of regression models is encountered during the analysis, the use of a risk score as a single summary confounder will be considered to adjust for multiple factors simultaneously.

Any confounders or effect modifiers that are included in the analyses and report but not identified in the protocol will be clearly identified in the report.

9.7.2.5 Analysis of Dose-Response Effect of Domperidone Use on Risk of SCD

Daily dose of current domperidone exposure will be categorised in mg per day values of < 30, 30, > 30 to ≤ 40, > 40 to ≤ 60, > 60 to ≤ 80 and > 80. Conditional logistic regression models will be constructed using these categories compared with the reference category of non-use of domperidone. Odds ratios will be computed adjusted for the matching variables only and adjusted for all covariates in the final multivariable model.

In addition, spline regression will be used to evaluate and describe the dose-response trend (Greenland, 1995; Boucher et al., 1998). In this method, all data points are used to estimate the shape of the dose-response trend, and separate curves are fit for segments of the dose-response distribution. With the use of categories, high-risk individuals can be unknowingly combined with lower-risk individuals leading to a dilution of the estimated size of the effect (Greenland, 1995). With spline regression, cut points or knots are chosen at either preset points or at points at which the form of the relationship is considered likely to change. The regression line segments meet at these knots and have identical slopes at the knot if the spline model is more than linear. For the current analysis, the cut points will be chosen such that they are in between the natural daily dose cut points for domperidone, which are 30 mg, 40 mg, 60 mg and 80 mg.

9.7.2.6 Stratified and Subgroup Analyses

Subgroup analyses will be performed for variables that could be possible effect modifiers (that is, different relationship of domperidone exposure to SCD exists according to the presence or absence of different categories of the variable). The data will be stratified by the presence or absence of the possible effect modifier and the effect estimates examined within each category. If the effect estimates differ by category, the conditional logistic regression model will be fitted with the appropriate interaction term(s). If strong evidence of effect modification is found, the analysis will be stratified into categories of

the variable, and separate conditional logistic regression models will be fit for each category. Possible variables to explore as effect modifiers are patient age, domperidone dose, diabetes status, chronic indications for use of domperidone, heart failure, ischaemic heart disease, and concomitant exposure to CYP3A4 inhibitor or QTc-prolonging medications. Variables that are evaluated but do not show evidence of effect modification will be included in the multivariable models as covariates as appropriate.

Subgroup analyses will be performed to investigate if the risk of SCD in patients with medical conditions used as a proxy of diabetic gastroparesis is different than that for the use of domperidone in other patients.

Subgroup analyses will be performed to investigate the risk of SCD in patients with medical conditions known to be strongly associated with drug-induced SVA, such as renal impairment or failure; severe chronic obstructive pulmonary disease; stroke; and recent acute myocardial infarction, stroke, or hospitalisation for heart failure. We will explore the completeness of laboratory data in the CPRD on electrolyte values within the month before the case/control index date to determine whether sufficient data are available to define hypokalemia, hypomagnesemia, and hyponatremia. If so, we will include these electrolyte imbalances as covariates in subgroup analyses. In addition, if sufficient data are available for drug abuse, we will perform a subgroup analysis on this variable.

9.7.3 Sensitivity Analyses

9.7.3.1 Case-Crossover Analysis

The nested case-control analysis is considered the primary analysis. To explore the impact of residual confounding by indication on the effect estimates, a case-crossover analysis will be performed as the main sensitivity analysis using all the SCD cases in the study. In this analysis, current exposure to domperidone at the time of SCD will be ascertained from the person-time of the cohort and will be compared with current exposure to domperidone in control time windows randomly selected from the at-risk person-time of each individual. A similar assessment of current exposure to each of the two comparison medications, PPIs and metoclopramide, at the time of SCD will be done.

In this analysis, the same person is both case and control, thus confounding by indication is reduced because the analysis eliminates between-person confounding by time-invariant characteristics including chronic medical conditions that could be indications for domperidone (Maclure, 1991; Schneeweiss et al., 1997; Wilson and Hawken, 2012). This type of design is useful for intermittent exposures such as domperidone. Some other within-person factors that are not available in the database and could be important confounding factors will be indirectly controlled with a case-crossover analysis. These include average physical activity levels, long-term diet and alcohol drinking patterns, regular use of non-prescription medications, habitual health behaviors, and smoking and body mass history (Maclure et al., 2012).

We will create matched sets using one case time window and three control time windows per case, selected before the outcome occurrence (unidirectional design). Control time windows will be equally spaced, and because the risk of death from cardiac disease varies by day of the week, control time windows will begin on the same day of the week as the case time window. There is some evidence of seasonal patterns in mortality from coronary heart disease (Seretakis et al., 1997). If evidence of seasonal trends in

domperidone prescribing is found in the CPRD database and a review of relevant literature reveals strong evidence of seasonal effects on SCD, control time windows will also be selected to correspond to the season of case time windows.

The frequency of current exposure to domperidone at the time of SCD, as well as the frequency of current domperidone exposure in the control time windows, will be determined. Similarly, the frequency of exposure to each of the comparison medications (PPIs and metoclopramide) in the case and control time windows will be determined. Conditional logistic regression will be performed on the matched sets. The OR with 95% confidence interval will be calculated separately for current domperidone exposure, current PPI exposure, and current metoclopramide exposure, and the effect estimates will be compared.

Bias in effect estimates from exposure time misclassification could occur in a case-crossover study of domperidone because domperidone is used sporadically by many patients and use can be in response to fluctuating symptoms (Maclure et al., 2012). The probability that an individual prescribed domperidone actually uses the medication is highest immediately after the prescription is filled, thus the choice of a cut-off date is important. A sensitivity analysis will be performed varying the length of the time windows for exposure. In addition, sensitivity analyses will be performed for time-varying factors that could differ between case and control time windows. For cases of SCD that occur shortly after cohort entry, it is possible that fewer than four comparison periods can be identified or no comparison period can be found. We will include all cases in the case-crossover analysis for whom at least one exposure window can be identified. If no comparison period is available for a case, this case will be excluded from the case-crossover analysis.

9.7.3.2 Other Sensitivity Analyses

Sensitivity analyses will be performed in which the risk will be explored in varying time windows after domperidone prescription. The risk in the 7 days after the prescription period, 7-14 days after the prescription period, 14-21 days after the prescription period and 21-30 days after the prescription period will be analyzed. These analyses will be conditional on having sufficient data to observe a systematic association, not random variation.

9.8   Quality Control

Standard operating procedures will be used to guide the conduct of key parts of the study. These SOPs include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

Analysis datasets and programme output will be checked for accuracy and integrity according to SOPs that include the following steps:

- Checking programme logs for errors and warnings

- Checking output for errors and inconsistencies

- Running quality-control programmes to verify that specifications were implemented correctly and that any output generated accurately reflects the data

- ▪ Manually reviewing output for a sample of study subjects to verify the classification of observed person-time and the assignment of cases

- ▪ Checking all results tables for accuracy

All key study documents, such as the SAP, the study report, abstract, and manuscript will undergo quality-control review, senior scientific review, and editorial review.

An independent Office of Quality Assurance (OQA) at RTI-HS will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry, data transfer, and institutional review board documentation. Such audits would be conducted by the OQA according to established criteria in SOPs and other applicable procedures.

9.9   Limitations of the Research Methods

Possible misclassification of the outcome, out-of-hospital SCD, could occur if the accuracy of diagnosis as recorded on death certificates, especially for unattended sudden death is poor. In some cases it may be necessary to examine the free text information for information on circumstances relating to the death to determine whether the death was sudden and unexpected.

Exposure misclassification could result because the CPRD includes prescribing information, but it is not known whether the prescription was filled or when or how it was actually taken by the patient. This could be particularly problematic for a drug like domperidone, in which the usual recommended dose is variable (i.e., 10 mg orally 3 to 4 times a day) and dosing can be increased quickly if adequate control of symptoms is not observed within a short period of time (i.e., 2 to 4 weeks), or it is prescribed on an "as needed" basis. For medications with 2 or more consecutive prescriptions, there is more certainty that the prescriptions were actually filled. In addition, domperidone and one PPI medication are available both by prescription and OTC in the UK. Over-the-counter drug use is not recorded in the CPRD, so it cannot be evaluated in a study of this type. Because the use of OTC medications in the UK is less common than use of prescription medications (British Medical Association, 2005), the extent of exposure misclassification due to unrecorded OTC use is likely to be small. In addition, while the cost of a packet of 10 tablets of OTC Motilium (domperidone) is slightly less than the cost of a prescription for Motilium, typically the number of tablets prescribed is higher than the number available in an OTC packet. Therefore, for usage other than very short-term, it is unlikely that NHS patients would preferentially choose an OTC preparation than a prescription. Although substantial differences between the characteristics of OTC users and prescription users are likely, the mechanisms of SCD in both groups are likely to be similar, so minimal bias is expected to persist after adjustment for these differences.

Arrhythmia-related deaths are generally agreed to be a "multiple hit" phenomenon, meaning that multiple factors occurring together trigger the development of a fatal arrhythmia. Thus, very accurately monitoring the risk is critical because residual confounding from unmeasured or incompletely measured factors would affect the results. Data on important risk factors for SCD such as smoking, BMI, and alcohol use are incomplete in the CPRD, recorded for only about 70% of patients (Gelfand et al., 2005), and data on exercise habits is not available. Also, other factors strongly related to

SCD risk, such as left ventricular ejection fraction, estimated glomerular filtration rate (an indicator of renal function), electrolyte disorders, and recreational drug use are not consistently recorded in the CPRD. The case-crossover analysis will provide some control for these time-varying factors and also for time-invariant factors. Information on strong triggers of drug-induced SVA—such as electrolyte disorders (digitalis toxicity, hypokalemia, hyperkalemia, or hypomagnesemia) and use of illicit or recreational drugs is not readily available, nor is information on the use of OTC medications such as aspirin for cardioprotection.

There is also a small risk of protopathic bias. Prodromic symptoms of heart disease could mimic those of gastrointestinal disease and be the reason for domperidone or other gastrointestinal medication prescription.

Information about disease severity is not systematically recorded in the CPRD, but in some instances can be derived from associated conditions, diagnoses, and treatments.

10 PROTECTION OF HUMAN SUBJECTS

Institutional review board approval and/or any other required reviews of the study protocol by specific committees will be obtained in accordance with applicable national and local regulations.

The final study protocol will be submitted to the Independent Scientific Advisory Committee (ISAC) of the CPRD as specified on the CPRD Web site (http://www.cprd.com/ISAC). The CPRD requires that any study using CPRD data that will be published or for which results will be communicated to third parties must receive ISAC approval before proceeding. The protocol submission process includes completing the CPRD ISAC application form, which is available online (http://www.cprd.com/ISAC).

The final protocol will also be submitted to the RTI institutional review board for review and approval.

10.1 Other Good Research Practice

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) (2007) Guidelines for Good Pharmacoepidemiology Practices (GPP), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2012). The ENCePP Study Protocol checklist will be completed (ENCePP, 2011).

The study will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC and its refinement provided in Chapter I.7 Section 1 of Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use (European Commission, 2008) and referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) harmonised tripartite guideline Pharmacovigilance Planning E2E (ICH, 2004) and the 2012 Guideline on Good Pharmacovigilance Practices (GVP), Module VIII – Post-Authorisation Safety Studies (European Medicines Agency [EMA], 2012a).

The study will be registered in the ENCePP electronic register of studies (ENCePP, 2010).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

For studies in which the research team uses data from automated health care databases only, according to the ISPE (2007) *Guidelines for Good Pharmacoepidemiology Practices (GPP)*,

> *"Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines."*

In accordance with the EMA Guideline on GVP, Module VI (EMA, 2012b, Section VI.C.1.2.1), for this non-interventional study that is based on secondary use of data and electronic health care records, reporting adverse reactions in an expedited manner to European Authorities is not required. Reports of adverse events/reactions will be summarised in the study report, where applicable

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, study progress and final study report(s) will be included in regulatory communications in line with the risk management plan, Periodic Safety Update Reports, and other regulatory milestones and requirements. Study reports will be prepared using a template following GVP Module VIII, Section VIII.B.6.3 (EMA, 2012a).

In its Guidelines for GPP, ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" (ISPE, 2007, Section V), for example, results pertaining to the safety of a marketed medication. Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (2010). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (STROBE, 2007).

Communication via appropriate scientific venues, such as ISPE, will be considered.

13 REFERENCES

Barone JA. Domperidone: a peripherally acting dopamine2-receptor antagonist. Ann Pharmacother. 1999;33(4):429-40.

Boucher KM, Slattery ML, Berry TD, Quesenberry C, Anderson K. Statistical methods in epidemiology: A comparison of statistical methods to analyze dose-response and trend analysis in epidemiologic studies. J Clin Epidemiol. 1998;51(12):1223-33.

British Medical Association, Board of Science. Over-the-counter medication. 2005. Available at: http://www.blenkinsopp.co.uk/BMAreportOTCmeds.pdf. Accessed 15 October 2012.

Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. Pharmacoepidemiol Drug Saf. 2010;19:563-72.

Domperidone summary of product characteristics. Updated 17 Nov 2011. Available at: http://www.medicines.org.uk/emc/medicine/18865. Accessed 10 September 2012.

Drolet B, Rousseau G, Daleau P, Cardinal R, Turgeon J. Domperidone should not be considered a no-risk alternative to cisapride in the treatment of gastrointestinal motility disorders. Circulation. 2000;102(16):1883-5.

European Commission. Volume 9A of the rules governing medicinal products in the European Union: guidelines on pharmacovigilance for medicinal products for human use. September 2008. Available at: http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm. Accessed 10 September 2012.

European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. 22 June 2012b. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf. Accessed 10 September 2012.

European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies. 9 July 2012a. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed 10 September 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Electronic register of studies. Version 3.0.46. 2010. Available at: http://www.encepp.eu/encepp/studiesDatabase.jsp. Accessed 12 September 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP checklist for study protocols (revision 1). 19 August 2011. Available at: http://www.encepp.eu/standards_and_guidances/index.html. Accessed 12 September 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology. 13 May 2012. Available at: http://www.encepp.eu/standards_and_guidances/index.html. Accessed 10 September 2012.

Gallagher AM, Smeeth L, Seabroke A, Leufkens HGM, van Staa TP. Risk of death and cardiovascular outcomes with thiazolidinediones: a study with the General Practice Research Database and secondary care data. PLoS One. 2011;6(12):e28157.

Gelfand JM, Margolis DJ, Dattani H. The UK General Practice Research Database. In: Strom BL, editor Pharmacoepidemiology, 4th edition. John Wiley & Sons; 2005. p. 337-46.

Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology. 1995;6:356-65.

Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69:4-14.

Huikuri H, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001;345:1473-82.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Pharmacovigilance planning. E2E. 2004. Available at: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/pharmacovigilance-planning.html. Accessed 10 September 2012.

International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. Updated April 2010. Available at: http://www.icmje.org/urm_main.html. Accessed 10 September 2012.

International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Revision 2. April 2007. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed 10 September 2012.

Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. Pharmacoepidemiol Drug Saf. 2010;19:881-8.

Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol. 1991;133(2):144-53.

Maclure M, Gireman B, Nelson JC, Hua W, Shoaibi A, Paredes A, et al. When should case-only designs be used for safety monitoring of medicinal products? Pharmacoepid Drug Saf. 2012;21(S1):50-61.

Medicines and healthcare products Regulatory Agency (MHRA). Domperidone: small risk of serious ventricular arrhythmia and sudden cardiac death. Drug Safety Update 2012 May;5(10):A2.

Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. Arch Gen Psychiatry. 2001 Dec;58(12):1161-7.

Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 2009;360:225-35.

Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and risk of sudden death from cardiac causes. N Engl J Med. 2004;351:1089-96.

Rossi M, Giorgi G. Domperidone and long QT syndrome. Curr Drug Saf. 2010;5:257-62.

Rothman KJ. Episheet—spreadsheets for the analysis of epidemiologic data. October 25, 2011, version. Available at http://www.epidemiolog.net/studymat/. Accessed 10 September 2012.

Schneeweiss S, Sturmer T, Maclure M. Case-crossover and case-time-control designs as alternatives in pharmacoepidemiologic research. Pharmacoepidemiol Drug Saf. 1997;6(suppl 3):S51-9.

Seretakis D, Lagiou P, Lipworth L, Signorello LB, Rothman KJ, Trichopoluos D. Changing seasonality of mortality from coronary heart disease. JAMA. 1997;278(12):1012-1014.

Setakis E, Gallagher A, Williams TW, van Staa TP. Linking UK death certificate data to UK primary care data (GPRD) to obtain cause of death. Pharmacoepidemiol Drug Saf. 2010;19:S83.

Shah AD, Martinez C. An algorithm to derive a numerical daily dose from unstructured text dosage instructions. Pharmacoepidemiol Drug Saf. 2006;15(3):161-6.

Straus SM, Sturkenboom MC, Bleumink GS, Dieleman JP, van der Lei J, de Graeff PA, et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. Eur Heart J. 2005;26(19):2007-12.

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. STROBE checklist. 2007. Available at: http://www.strobe-statement.org/index.php?id=available-checklists. Accessed 10 September 2012.

van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. Pharmacoepidemiol Drug Saf. 2010;33(11):1003-14.

Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. J Thromb Haemost. 2011;9(1):39-48.

Wilson K, Hawken S. Drug safety studies and measures of effect using the self-controlled case series design. Pharmacoepidemiol Drug Saf. 2012: DPI: 10.1002/pds.3337.

Annexes:
Medication Codes in the CPRD for Domperidone, PPIs, and Metoclopramide

Table 4.   Codes for Domperidone Products in the CPRD

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
1020	3685001	Domperidone tablets 10mg	Domperidone maleate	10 mg	Tablets	Oral
1396	3685003	Domperidone suspension 5mg/5ml	Domperidone	5 mg/5 ml	Suspension	Oral
2254	1291001	MOTILIUM tablets 10mg	Domperidone maleate	10 mg	Tablets	Oral
4136	3685002	Domperidone suppository 30mg	Domperidone	30 mg	Suppository	Rectal
9077	602001	MOTILIUM sugar-free suspension 1mg/ml	Domperidone	1 mg/ml	Sugar-free suspension	Oral
9476	11222001	DOMPERAMOL tablets 500mg + 10mg	Domperidone maleate/ paracetamol	500 mg + 10 mg	Tablets	Oral
8066	602002	MOTILIUM suppository 30mg	Domperidone	30 mg	Suppository	Rectal
11614	11221001	Paracetamol with domperidone tablets 500mg + 10mg	Domperidone maleate/ paracetamol	500 mg + 10 mg	Tablets	Oral
9519	7454001	MOTILIUM 10 tablets	Domperidone maleate		Tablets	Oral
15092	2938001	EVOXIN tablets 10mg	Domperidone maleate	10 mg	Tablets	Oral
26177	2829009	DOMPERIDONE tablets 10mg	Domperidone maleate	10 mg	Tablets	Oral
44292	16204001	Domperidone orodispersible tablet 10mg	Domperidone maleate	10 mg	Orodispersible tablet	Oral
29216	2174009	DOMPERIDONE tablets 10mg	Domperidone maleate	10 mg	Tablets	Oral
14443	2940001	EVOXIN suppository 30mg	Domperidone	30 mg	Suppository	Rectal
30176	3096009	DOMPERIDONE tablets 10mg	Domperidone maleate	10 mg	Tablets	Oral
44603	18110001	MOTILIUM INSTANTS orodispersible tablet	Domperidone maleate		Orodispersible tablet	Oral
45355	3194009	DOMPERIDONE tablets 10mg	Domperidone maleate	10 mg	Tablets	Oral

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
43710	7333009	DOMPERIDONE suspension 5mg/5ml	Domperidone	5 mg/5 ml	Suspension	Oral
32971	10650001	VIVADONE tablets 10mg	Domperidone maleate	10 mg	Tablets	Oral
43558	4264009	DOMPERIDONE tablets 10mg	Domperidone maleate	10 mg	Tablets	Oral
45644	3913009	DOMPERIDONE tablets 10mg	Domperidone maleate	10 mg	Tablets	Oral

CPRD = Clinical Practice Research Datalink.

Table 5. Codes for Proton Pump Inhibitor Medications in the CPRD

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
18	5588001	Omeprazole gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
30	7262002	Lansoprazole capsules of enteric coated granules 15mg	Lansoprazole	15 mg	Capsules of enteric-coated granules	Oral
39	7262001	Lansoprazole capsules of enteric coated granules 30mg	Lansoprazole	30 mg	Capsules of enteric-coated granules	Oral
89	5588003	Omeprazole gastro-resistant capsules 10mg	Omeprazole	10 mg	Gastro-resistant capsules	Oral
5178	11034001	Esomeprazole gastro-resistant tablets 20mg	Esomeprazole magnesium	20 mg	Gastro-resistant tablets	Oral
2151	10617002	Rabeprazole gastro-resistant tablets 20mg	Rabeprazole sodium	20 mg	Gastro-resistant tablets	Oral
1451	5588002	Omeprazole gastro-resistant capsules 40mg	Omeprazole	40 mg	Gastro-resistant capsules	Oral
1232	5587001	LOSEC capsules 20mg	Omeprazole	20 mg	Capsules	Oral
1977	10617001	Rabeprazole gastro-resistant tablets 10mg	Rabeprazole sodium	10 mg	Gastro-resistant tablets	Oral

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
5604	11034002	Esomeprazole gastro-resistant tablets 40mg	Esomeprazole magnesium	40 mg	Gastro-resistant tablets	Oral
5419	10211003	Pantoprazole enteric coated tablets 20mg	Pantoprazole sodium sesquihydrate	20 mg	Enteric-coated tablets	Oral
1986	10211001	Pantoprazole enteric coated tablets 40mg	Pantoprazole sodium sesquihydrate	40 mg	Enteric-coated tablets	Oral
6300	10843001	Lansoprazole orodispersible gastro-resistant tablet 30mg	Lansoprazole	30 mg	Orodispersible gastro-resistant tablet	Oral
6245	10810001	Lansoprazole orodispersible gastro-resistant tablet 15mg	Lansoprazole	15 mg	Orodispersible gastro-resistant tablet	Oral
6114	7657001	Omeprazole gastro-resistant tablets 20mg	Omeprazole	20 mg	Gastro-resistant tablets	Oral
4921	7553002	Omeprazole dispersible tablet 20mg	Omeprazole magnesium	20 mg	Dispersible tablet	Oral
519	7261001	ZOTON capsules 30mg	Lansoprazole	30 mg	Capsules	Oral
276	5587003	LOSEC capsules 10mg	Omeprazole	10 mg	Capsules	Oral
1947	7261002	ZOTON capsules 15mg	Lansoprazole	15 mg	Capsules	Oral
5232	7553001	Omeprazole dispersible tablet 10mg	Omeprazole magnesium	10 mg	Dispersible tablet	Oral
5269	7866001	NEXIUM tablets 20mg	Esomeprazole magnesium	20 mg	Tablets	Oral
6727	10229001	PROTIUM enteric coated tablets 40mg	Pantoprazole sodium sesquihydrate	40 mg	Enteric-coated tablets	Oral
9851	7656001	Omeprazole gastro-resistant tablets 10mg	Omeprazole	10 mg	Gastro-resistant tablets	Oral
6490	7866002	NEXIUM tablets 40mg	Esomeprazole magnesium	40 mg	Tablets	Oral
3979	7924001	HELICLEAR triple pack 500mg + 500mg + 30mg	Amoxicillin trihydrate/clarithromycin/lansoprazole	500 mg + 500 mg + 30 mg	Triple pack	Oral

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
6063	9928001	ZOTON FasTab 30mg	Lansoprazole	30 mg	FasTab	Oral
6165	10229002	PROTIUM enteric coated tablets 20mg	Pantoprazole sodium sesquihydrate	20 mg	Enteric-coated tablets	Oral
1941	10620002	PARIET enteric coated tablets 20mg	Rabeprazole sodium	20 mg	Enteric-coated tablets	Oral
5358	7262003	Lansoprazole gastro-resistant granules for oral suspension 30mg	Lansoprazole	30 mg	Gastro-resistant granules for oral suspension	Oral
35698	14486001	MEPRADEC gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
5236	9421002	LOSEC MUPS tablets 20mg	Omeprazole magnesium	20 mg	Tablets	Oral
5834	10620001	PARIET enteric coated tablets 10mg	Rabeprazole sodium	10 mg	Enteric-coated tablets	Oral
6291	9590001	ZOTON FasTab 15mg	Lansoprazole	15 mg	FasTab	Oral
9989	10574001	Omeprazole gastro-resistant tablets 40mg	Omeprazole	40 mg	Gastro-resistant tablets	Oral
4654	5587002	LOSEC capsules 40mg	Omeprazole	40 mg	Capsules	Oral
4955	7553003	Omeprazole dispersible tablet 40mg	Omeprazole magnesium	40 mg	Dispersible tablet	Oral
5662	7926001	Amoxicillin with clarithromycin and lansoprazole triple pack 500mg + 500mg + 30mg	Amoxicillin trihydrate/clarithromycin/ lansoprazole	500 mg + 500 mg + 30 mg	Triple pack	Unknown
13015	9421001	LOSEC MUPS tablets 10mg	Omeprazole magnesium	10 mg	Tablets	Oral
35699	14485001	MEPRADEC gastro-resistant capsules 10mg	Omeprazole	10 mg	Gastro-resistant capsules	Oral
7255	13974001	Omeprazole oral suspension 20mg/5ml	Omeprazole	20 mg/5 ml	Oral suspension	Oral
35101	15395001	Omeprazole oral suspension 10mg/5ml	Omeprazole	10 mg/5 ml	Oral suspension	Oral
13282	13883001	Omeprazole oral suspension 5mg/5ml	Omeprazole	5 mg/5 ml	Oral suspension	Oral

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
10098	7261003	ZOTON granules for suspension 30mg	Lansoprazole	30 mg	Granules for suspension	Oral
6256	1689001	HELIMET triple pack	Metronidazole/ clarithromycin/lansoprazole		Triple pack	Oral
29457	4068009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
32924	4064009	OMEPRAZOLE tablets 20mg	Omeprazole	20 mg	Tablets	Oral
9825	9421003	LOSEC MUPS tablets 40mg	Omeprazole magnesium	40 mg	Tablets	Oral
43948	18019001	Esomeprazole gastro-resistant capsules 40mg	Esomeprazole magnesium	40 mg	Gastro-resistant capsules	Oral
43995	18018001	Esomeprazole gastro-resistant capsules 20mg	Esomeprazole magnesium	20 mg	Gastro-resistant capsules	Oral
34841	4091009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
41364	17452001	Ketoprofen with omeprazole modified release capsules 100mg + 20mg	Ketoprofen/omeprazole	100 mg + 20 mg	Modified-release capsules	Oral
41366	17454001	AXORID modified release capsules 100mg + 20mg	Ketoprofen/omeprazole	100 mg + 20 mg	Modified-release capsules	Oral
36892	4054009	OMEPRAZOLE tablets 10mg	Omeprazole	10 mg	Tablets	Oral
6497	781001	Clarithromycin with metronidazole and lansoprazole triple pack 500mg + 400mg + 30mg	Metronidazole/ clarithromycin/lansoprazole	500 mg + 400 mg + 30 mg	Triple pack	Unknown
41367	17453001	Ketoprofen with omeprazole modified release capsules 200mg + 20mg	Ketoprofen/omeprazole	200 mg + 20 mg	Modified-release capsules	Oral
41365	17455001	AXORID modified release capsules 200mg + 20mg	Ketoprofen/omeprazole	200 mg + 20 mg	Modified-release capsules	Oral
30926	4067009	OMEPRAZOLE gastro-resistant capsules 10mg	Omeprazole	10 mg	Gastro-resistant capsules	Oral
42532	6381009	LANSOPRAZOLE capsules 30mg	Lansoprazole	30 mg	Capsules	Oral

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
34302	4019009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
15290	11992001	Lansoprazole with amoxicillin and clarithromycin triple pack 30mg + 500mg + 500mg	Amoxicillin trihydrate/clarithromycin/lansoprazole	30 mg + 500 mg + 500 mg	Triple pack	Unknown
44800	18254001	Naproxen with esomeprazole modified release tablet 500mg + 20mg	Naproxen/esomeprazole	500 mg + 20 mg	Modified release tablet	Oral
43057	6359009	LANSOPRAZOLE capsules 30mg	Lansoprazole	30 mg	Capsules	Oral
34411	4012009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
42900	4072009	OMEPRAZOLE tablets 20mg	Omeprazole	20 mg	tablets	Oral
41501	17404001	Esomeprazole gastro-resistant granules for oral suspension 10mg	Esomeprazole magnesium	10 mg	Gastro-resistant granules for oral suspension	Oral
44986	18255001	VIMOVO modified release tablet 500mg + 20mg	Naproxen/esomeprazole	500 mg + 20 mg	Modified release tablet	Oral
42091	4055009	OMEPRAZOLE tablets 20mg	Omeprazole	20 mg	Tablets	Oral
42898	4082009	OMEPRAZOLE tablets 10mg	Omeprazole	10 mg	Tablets	Oral
15275	4011009	OMEPRAZOLE gastro-resistant capsules 10mg	Omeprazole	10 mg	Gastro-resistant capsules	Oral
11433	11991001	Clarithromycin with lansoprazole and amoxicillin triple pack 500mg + 30mg + 500mg	Amoxicillin trihydrate/clarithromycin/lansoprazole	500 mg + 30 mg + 500 mg	Triple pack	Unknown
26537	11951001	OMERAN tablets 20mg	Omeprazole	20 mg	Tablets	Oral

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
29835	11583001	Omeprazole powder for concentrate for solution for infusion 40mg	Omeprazole sodium	40 mg	Powder for concentrate for solution for infusion	Intravenous infusion
33326	4071009	OMEPRAZOLE tablets 10mg	Omeprazole	10 mg	Tablets	Oral
42730	6383009	LANSOPRAZOLE capsules 30mg	Lansoprazole	30 mg	Capsules	Oral
37815	6310009	LANSOPRAZOLE capsules 30mg	Lansoprazole	30 mg	Capsules	Oral
33565	6610009	OMEPRAZOLE caplets 20mg	Omeprazole	20 mg	Caplets	Oral
42736	4403009	OMEPRAZOLE tablets 20mg	Omeprazole	20 mg	Tablets	Oral
29468	4069009	OMEPRAZOLE gastro-resistant capsules 40mg	Omeprazole	40 mg	Gastro-resistant capsules	Oral
40759	6299009	LANSOPRAZOLE capsules 15mg	Lansoprazole	15 mg	Capsules	Oral
25245	11583002	Omeprazole powder for solution for injection 40mg	Omeprazole sodium	40 mg	Powder for solution for injection	Intravenous injection
35383	4994009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
33873	9369001	LOSEC IV injection 40mg	Omeprazole sodium	40 mg	Injection	Intravenous injection
18225	12390001	Esomeprazole powder for solution for injection 40mg/vial	Esomeprazole	40 mg/vial	Powder for solution for injection	Intravenous Injection
31213	6909001	OMERAN tablets 10mg	Omeprazole	10 mg	Tablets	Oral
34568	4018009	OMEPRAZOLE gastro-resistant capsules 10mg	Omeprazole	10 mg	Gastro-resistant capsules	Oral
46744	18020001	EMOZUL gastro-resistant capsules 20mg	Esomeprazole magnesium	20 mg	Gastro-resistant capsules	Oral
43957	6604009	OMEPRAZOLE tablets 20mg	Omeprazole	20 mg	Tablets	Oral
46745	18021001	EMOZUL gastro-resistant capsules 40mg	Esomeprazole magnesium	40 mg	Gastro-resistant capsules	Oral

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
17111	10211002	Pantoprazole lyophilised powder for injection 40mg	Pantoprazole sodium sesquihydrate	40 mg	Lyophilised powder for injection	Intravenous injection
34791	4020009	OMEPRAZOLE gastro-resistant capsules 40mg	Omeprazole	40 mg	Gastro-resistant capsules	Oral
34843	4046009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
42533	5797009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
35257	4995009	OMEPRAZOLE gastro-resistant capsules 40mg	Omeprazole	40 mg	Gastro-resistant capsules	Oral
33022	12439001	ZANPROL tablets 10mg	Omeprazole	10 mg	Tablets	Oral
34571	4021009	OMEPRAZOLE gastro-resistant capsules 10mg	Omeprazole	10 mg	Gastro-resistant capsules	Oral
41454	17405001	NEXIUM gastro-resistant granules for oral suspension 10mg	Esomeprazole magnesium	10 mg	Gastro-resistant granules for oral suspension	Oral
34577	4022009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
34332	4090009	OMEPRAZOLE gastro-resistant capsules 10mg	Omeprazole	10 mg	Gastro-resistant capsules	Oral
44023	17757001	PANTOLOC CONTROL enteric coated tablets 20mg	Pantoprazole sodium sesquihydrate	20 mg	Enteric-coated tablets	Oral
45173	6652009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
22709	11584001	LOSEC infusion 40mg	Omeprazole sodium	40 mg	Infusion	Intravenous infusion
34812	4280009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
34967	4081009	OMEPRAZOLE gastro-resistant capsules 20mg	Omeprazole	20 mg	Gastro-resistant capsules	Oral
39904	6309009	LANSOPRAZOLE capsules 15mg	Lansoprazole	15 mg	Capsules	Oral
44252	6486009	OMEPRAZOLE oral suspension 20mg/5ml	Omeprazole	20 mg/5 ml	Oral suspension	Oral
25596	12391001	NEXIUM powder for solution for injection 40mg/vial	Esomeprazole	40 mg/vial	Powder for solution for injection	Intravenous injection
36046	4013009	OMEPRAZOLE gastro-resistant capsules 40mg	Omeprazole	40 mg	Gastro-resistant capsules	Oral
42114	10178001	OMERAN tablets 40mg	Omeprazole	40 mg	Tablets	Oral
32919	4060009	OMEPRAZOLE tablets 20mg	Omeprazole	20 mg	Tablets	Oral
29422	11584002	LOSEC injection 40mg	Omeprazole sodium	40 mg	Injection	Unknown
32914	4063009	OMEPRAZOLE tablets 10mg	Omeprazole	10 mg	Tablets	Oral
40896	6300009	LANSOPRAZOLE capsules 30mg	Lansoprazole	30 mg	Capsules	Oral
41992	6653009	OMEPRAZOLE tablets 10mg	Omeprazole	10 mg	Tablets	Oral
44753	6402009	LANSOPRAZOLE capsules 30mg	Lansoprazole	30 mg	Capsules	Oral
24360	12555001	HEARTBURN RELIEF tablets 10mg	Omeprazole	10 mg	Tablets	Oral
34792	4080009	OMEPRAZOLE gastro-resistant capsules 10mg	Omeprazole	10 mg	gastro-resistant capsules	Oral
42382	7685009	LANSOPRAZOLE capsules 30mg	Lansoprazole	30 mg	Capsules	Oral
34984	12686001	HEARTBURN RELIEF tablets 10mg	Omeprazole	10 mg	Tablets	Oral
44700	7374001	PROTIUM IV lyophilised powder for injection 40mg	Pantoprazole sodium sesquihydrate	40 mg	Lyophilised powder for injection	Intravenous injection

CPRD = Clinical Practice Research Datalink.

Table 6. Metoclopramide-Containing Medications in the CPRD

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
455	4162001	Metoclopramide tablets 10mg	Metoclopramide hydrochloride	10 mg	Tablets	Oral
892	1641001	PARAMAX tablets	Metoclopramide hydrochloride/paracetamol		Tablets	Oral
511	555001	MAXOLON tablets 10mg	Metoclopramide hydrochloride	10 mg	Tablets	Oral
890	1641002	PARAMAX sachets	Metoclopramide hydrochloride/paracetamol		Sachets	Oral
2306	5075001	Paracetamol with metoclopramide tablets 500mg+5mg	Metoclopramide hydrochloride/paracetamol	500 mg+5 mg	Tablets	Oral
5081	5899001	Metoclopramide sugar free solution 5mg/5ml	Metoclopramide hydrochloride	5 mg/5 ml	Sugar-free solution	Oral
1724	555002	MAXOLON syrup 5mg/5ml	Metoclopramide hydrochloride	5 mg/5 ml	Syrup	Oral
405	5545002	Metoclopramide modified release capsules 15mg	Metoclopramide hydrochloride	15 mg	Modified-release capsules	Oral
4142	5187001	Metoclopramide syrup 5mg/5ml	Metoclopramide hydrochloride	5 mg/5 ml	Syrup	Oral
3514	5075002	Paracetamol with metoclopramide sachets 500mg+5mg	Metoclopramide hydrochloride/paracetamol	500 mg+5 mg	Sachets	Oral
8273	5168001	GASTROBID CONTINUS tablets 15mg	Metoclopramide hydrochloride	15 mg	Tablets	Oral
179	555003	MAXOLON injection 10mg/2ml	Metoclopramide hydrochloride	10 mg/2 ml	Injection	Intravenous injection
3155	577001	MIGRAVESS effervescent tablet 5mg + 325mg	Aspirin/citric acid/ metoclopramide hydrochloride/ sodium bicarbonate	5 mg + 325 mg	Effervescent tablet	Oral
299	5187003	Metoclopramide injection 10mg/2ml	Metoclopramide hydrochloride	10 mg/2 ml	Injection	Intravenous injection

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
3386	1719001	MIGRAVESS FORTE effervescent tablet 5mg + 450mg	Aspirin/citric acid/ metoclopramide hydrochloride/ sodium bicarbonate	5 mg + 450 mg	Effervescent tablet	Oral
4892	4162002	Metoclopramide tablets 5mg	Metoclopramide hydrochloride	5 mg	Tablets	Oral
35046	15348001	Metoclopramide injection 10mg/2ml	Metoclopramide hydrochloride	10 mg/2 ml	Injection	Intravenous injection
5288	515001	MIGRAMAX powder for oral solution 900mg + 10mg	Aspirin lysine/ metoclopramide hydrochloride	900 mg + 10 mg	Powder for oral solution	Oral
3716	5488001	Metoclopramide modified release tablet 15mg	Metoclopramide hydrochloride	15 mg	Modified-release tablet	Oral
15601	5830001	MAXOLON SR capsules 15mg	Metoclopramide hydrochloride	15 mg	Capsules	Oral
8386	1640001	MAXOLON PAEDIATRIC sugar free liquid 1mg/ml	Metoclopramide hydrochloride	1 mg/ ml	Sugar-free liquid	Oral
304	11074001	MAXOLON tablets 5mg	Metoclopramide hydrochloride	5 mg	Tablets	Oral
12976	68001	Lysine acetylsalicylate with metoclopramide powder for oral solution 900mg + 10mg	Aspirin lysine/ metoclopramide hydrochloride	900 mg + 10 mg	Powder for oral solution	Oral
6521	5187002	Metoclopramide sugar free liquid 1mg/ml	Metoclopramide hydrochloride	1 mg/ ml	Sugar-free liquid	Oral
8525	784001	PRIMPERAN tablets 10mg	Metoclopramide hydrochloride	10 mg	Tablets	Oral
17496	5726001	GASTROFLUX tablets 10mg	Metoclopramide hydrochloride	10 mg	Tablets	Oral
39621	16942001	MAXOLON tablets 10mg	Metoclopramide hydrochloride	10 mg	Tablets	Oral
17946	5546001	GASTROMAX sustained release capsules 30mg	Metoclopramide hydrochloride	30 mg	Sustained-release capsules	Oral

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
17180	4165002	Metoclopramide with aspirin effervescent tablet 5mg + 450mg	Aspirin/citric acid/ metoclopramide hydrochloride/ sodium bicarbonate	5 mg + 450 mg	Effervescent tablet	Oral
3726	4165001	Metoclopramide with aspirin effervescent tablet 5mg + 325mg	Aspirin/citric acid/ metoclopramide hydrochloride/ sodium bicarbonate	5 mg + 325 mg	Effervescent tablet	Oral
39653	16944001	MAXOLON injection 10mg/2ml [AMDIPHARM]	Metoclopramide hydrochloride	10 mg/2 ml	Injection	Intravenous injection
33229	1512009	METOCLOPRAMIDE tablets 10mg	Metoclopramide hydrochloride	10 mg	Tablets	Oral
12778	4167001	Metoclopramide with paracetamol tablets 5mg + 500mg	Metoclopramide hydrochloride/paracetamol	5 mg + 500 mg	Tablets	Oral
17832	5545001	Metoclopramide modified release capsules 30mg	Metoclopramide hydrochloride	30 mg	Modified-release capsules	Oral
39710	16943001	MAXOLON syrup 5mg/5ml	Metoclopramide hydrochloride	5 mg/5 ml	Syrup	Oral
9118	784002	PRIMPERAN sugar free syrup 5mg/5ml	Metoclopramide hydrochloride	5 mg/5 ml	Sugar-free syrup	Oral
16567	4164001	Metoclopramide high dose concentrate for solution for infusion 100mg/20ml	Metoclopramide hydrochloride	100 mg/20 ml	Concentrate for solution for infusion	Intravenous infusion
26363	495009	METOCLOPRAMIDE tablets 10mg	Metoclopramide hydrochloride	10 mg	Tablets	Oral
14844	4171001	MAXOLON HIGH DOSE concentrate for solution for infusion 100mg/20ml	Metoclopramide hydrochloride	100 mg/20 ml	Concentrate for solution for infusion	Intravenous infusion
12869	4167002	Metoclopramide with paracetamol sachets 5mg + 500mg	Metoclopramide hydrochloride/paracetamol	5 mg + 500 mg	Sachets	Oral

Product Code	Multilex Code	Product Name	Drug Substance Name	Substance Strength	Formulation	Route of Administration
21863	5517001	GASTRESE LA controlled release tablet 15mg	Metoclopramide hydrochloride	15 mg	Controlled-release tablet	Oral
11576	7774001	METOCLOMEX tablets 10mg	Metoclopramide hydrochloride	10 mg	Tablets	Oral
13034	2746009	METOCLOPRAMIDE injection 5mg/ml	Metoclopramide hydrochloride	5 mg/ ml	Injection	Intravenous injection
25992	3298009	METOCLOPRAMIDE syrup 5mg/5ml	Metoclopramide hydrochloride	5 mg/5 ml	Syrup	Oral
17456	1690001	Metoclopramide with lysine acetylsalicylate powder for oral solution 10mg + 900mg	Aspirin lysine/ metoclopramide hydrochloride	10 mg + 900 mg	Powder for oral solution	Oral
23753	784003	PRIMPERAN injection 5mg/ml	Metoclopramide hydrochloride	5 mg/ ml	Injection	Unknown
34084	1876009	METOCLOPRAMIDE injection 10mg/2ml	Metoclopramide hydrochloride	10 mg/2 ml	Injection	Intravenous injection
34325	497009	METOCLOPRAMIDE tablets 10mg	Metoclopramide hydrochloride	10 mg	Tablets	Oral
34887	494009	METOCLOPRAMIDE tablets	Metoclopramide hydrochloride	10 mg	Tablets	Oral
43448	15225001	Metoclopramide oral liquid	Metoclopramide hydrochloride		Oral liquid	Oral
25994	1935009	METOCLOPRAMIDE sugar free solution 5mg/5ml	Metoclopramide hydrochloride	5 mg/5 ml	Sugar-free solution	Oral
8784	4168001	METOX tablets 10mg	Metoclopramide hydrochloride	10 mg	Tablets	Oral

CPRD = Clinical Practice Research Datalink.