A Post-Authorisation Safety Study (PASS) Protocol

Title	A Drug Utilisation Study of Domperidone in Europe Using Databases
Protocol version identifier	Version 2: 20 July 2016
Date of last version of protocol	Version 1: 3 March 2016
EU PAS register number	Study not registered, but will be registered upon approval of the protocol
Active substance	Domperidone
Medicinal product	Domperidone
Product reference	ATC code:A03FA03
Procedure number	EMEA/H/N/PSP/J/0031
Marketing authorisation holder(s)	Janssen Research & Development on behalf of the Domperidone Collaboration Study Group (a group of all MAHs involved in the Consortium)
Joint PASS	Yes
Research question and objectives	The objective of the study is to investigate the effectiveness of risk minimisation measures and to describe the prescribing patterns before and after the changes to the domperidone label in routine clinical practice in selected European countries regarding the following measures: 1. Maximum daily dose (30 mg for adults, 0.25 mg/kg TID for children) 2. Concomitant medications that prolong the QT-interval or are potent CYP3A4 inhibitors 3. Prescribing to patients with contraindicated conditions, e.g., moderate or severe liver disease, underlying cardiac diseases 4. Prescribing for label indication 5. Prescribing for off-label indications 6. Length of treatment (greater than 7 days)
Country(-ies) of study	France, Germany, United Kingdom, Belgium, and Spain
Author	The DUS protocol subcommittee of the Domperidone Collaboration Study Group

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	Janssen Research & Development on behalf of the Domperidone Collaboration Study Group
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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

ADR	adverse drug reaction
CHMP	Committee for Human Medicinal Products
CPRD	Clinical Practice Research Datalink
DHPC	Direct Healthcare Professional Communication
EMA	European Medicines Agency
EU PAS Register	The electronic ENCePP E-Register of Studies (available at: http://www.encepp.eu/encepp/studiesDatabase.jsp)
FAMHP	Federal Agency for Medicines and Health Products
GERD	Gastro-oesophageal reflux disease
IBS	inflammatory bowel syndrome – also known as inflammatory bowel disease
LPD	Longitudinal Patients Database
MAH(s)	Marketing Authorisation Holder(s)
NDD	numerical daily dose
OMOP CDM	Observational Medical Outcomes Partnership Common Data Model
PhVWP	EU Pharmacovigilance Working Party
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PRN	pro re nata (as needed)
SmPC	Summary of Product Characteristics

3. RESPONSIBLE PARTIES

The main responsible parties are presented in Table 1.

Table 1: List of All Main Responsible Parties

Responsible Party	Name and Affiliation
Consortium	Domperidone Collaboration Study Group (for full membership, please refer to Annex 1).
Sponsor	Janssen Research & Development on behalf of the Domperidone Collaboration Study Group (a group of all MAHs involved in the Consortium)
Principal / Coordinating Investigator	Daniel Fife, MD Senior Director, Janssen PRD Department of Epidemiology

4. ABSTRACT

Title of Study

A Drug Utilisation Study of Domperidone in Europe Using Databases

Rationale and Background

In March 2013, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) initiated a review of domperidone-containing medicines at the request of the Federal Agency for Medicines and Health Products (FAMHP), under Article 31 of Directive 2001/83/EC over concerns about cardiac adverse effects of domperidone. Subsequently, PRAC recommended that the product label (Summary of Product Characteristics/SmPC and Patient Information Leaflet/PIL) of domperidone-containing medicines be updated to strengthen the information regarding cardiac risks. In addition, PRAC raised concerns that there may be off-label use of domperidone for the stimulation of lactation in breastfeeding women, for the treatment of gastro-oesophageal reflux disease (GERD), for the treatment of diabetic and non-diabetic gastroparesis, and for the treatment of symptoms of postural hypotension in Parkinson's patients. More recently the EMA asked that inflammatory bowel syndrome (IBS) be included in the present study as an off-label indication.

The recommended changes following conclusion of the Article 31 referral included the following:

- restriction of the indication to nausea and vomiting;
- limitation of duration of use to 7 days;
- reduction of the maximum daily dose to 10 mg TID for adults and adolescents (12 years of age and older and weighing 35 kg or more);
- reduction of the maximum daily dose to 0.25 mg/kg TID for neonates, infants, children (less than 12 years of age), and adolescents weighing less than 35 kg;
- contraindication of the combination with other drugs that increase the cardiac risks by themselves or increase the plasma level of domperidone; and
- contraindication in patients with moderate or severe hepatic impairment or certain cardiac conditions.

Within the context of risk minimisation measures, PRAC requested that domperidone MAHs perform a drug utilisation study to assess the effectiveness of the above mentioned risk minimisation measures and to monitor the off-label use of the drug. In addition to a physician survey proposed by the MAHs to assess the prescribers' knowledge of the new label of domperidone, EMA suggested the use of a healthcare database as an additional data source to measure domperidone utilisation patterns. This protocol describes a drug utilisation study using healthcare databases in 5 European Union countries.

Research Questions and Objectives

The objective of the study is to investigate the effectiveness of risk minimisation measures and describe prescribing patterns of domperidone, including those pertaining to the off-label use of domperidone, in routine clinical practice in 5 European Union countries.

Primary Objectives: To describe the prescribing patterns before and after the changes to the domperidone label and estimate and compare the overall proportion of domperidone prescriptions before and after implementation of the risk minimisation measures regarding the following measures:

- Composite endpoint consisting of the following components:
  - Maximum daily dose;
  - Duration of use (>7 days)
  - Concomitant medications that prolong the QT-interval or are potent CYP3A4 inhibitors;
  - Prescribing to patients with contraindicated conditions, e.g., moderate or severe liver disease, underlying cardiac diseases; and
  - Prescribing for off-label indications

Secondary Objectives: To estimate the overall proportion of domperidone prescriptions before and after implementation of the risk minimisation measures for domperidone for each of the components of the composite endpoint individually, the time trend of apparent indication, and days supplied (≤7 days vs. >7 days), and the age and sex of the people receiving prescriptions.

Study Design

This is a post-authorisation, retrospective, observational cohort study using a pre- and post-design to examine the changes in the prescribing patterns. A cohort of patients initiating domperidone will be identified from existing secondary data sources (IMS, CPRD) in selected European Union countries (France, Germany, United Kingdom, Belgium, and Spain). These countries are selected to provide a range of domperidone usage (from France, which has the highest per capita domperidone use in the EU, to Germany, which ranks number 12 in the EU for per capita domperidone use), and based on the availability of robust longitudinal electronic medical records databases. These data sources will include person-level information on demographics, prescriptions, and diagnoses.

Population

Defined as all patients receiving domperidone in the outpatient setting during the pre-defined periods (pre- and post- implementation periods of the risk minimisation activity) in the selected European Union countries (France, Germany, United Kingdom, Belgium, and Spain). Patients will be included in the study cohort if they have at least 1 prescription for domperidone in the selected databases during the pre-defined periods, and have been registered with the practice and have available medical history for at least 180 days.

Variables

Demographic characteristics (including age, sex, and geographic region); indication; dose per day; use in patients with contraindicated conditions; concurrent use with drug that prolong the QT interval or are potent or strong CYP3A inhibitors, and length of treatment will be examined.

Data Sources

Subject to change based on data availability, patient information on domperidone exposure and study endpoints will be obtained from Longitudinal Electronic Medical Records (EMR) databases, including IMS® Disease Analyzer and CPRD. These are described in Annex 5.

Study Size

The study size will vary according to country and data source. All patients available in the study population will be considered for the analysis. Preliminary estimates indicate that the suggested databases capture at least several thousands of domperidone prescriptions in each of the countries being studied.

Data Analysis

Data analysis in the study will be descriptive. Continuous variables will be presented using appropriate descriptive statistics, such as mean, median, standard deviation and range. Categorical variables will be presented using percent and frequency tables. The rates and 95% CI of all study endpoints (i.e., risk minimisation indicators) will be calculated for the 2011-2015 period, using quarterly time blocks for the pre- and post- risk minimisation implementation periods. The rates will be calculated per 1000 domperidone-treated patients or as percentage of domperidone prescriptions, as appropriate. Paediatric data will be described separately from adult patients and rate of paediatric use will be calculated as fraction of overall domperidone utilisation. All data analysis will be done in SAS using the version that is current when the analyses are done.

The rates for the primary endpoints of the study as the proportion of all prescriptions that are consistent with the revised label will be calculated:

1. Prescription for nausea and vomiting, or unknown indication but no recent diagnosis of GERD, gastroparesis, inflammatory bowel syndrome (IBS), symptoms of postural hypotension in Parkinson patients or as an aid to lactation;
2. Dose no higher than recommended;
3. No prescription to patients with certain cardiac and hepatic conditions; and
4. No co-prescription with CYP3A4 inhibitors or QT-prolonging drugs.

Note that additional analyses described in Section 9.3 will address the possibility that an unknown indication may be off-label, and the possibility that domperidone may be used for the entire number of days supplied.

Rates of the study endpoints will be assessed for the 1-year pre-implementation period (1 April 2013 through 31 March 2014) and will be compared with the 1-year post-implementation period (1 October 2014 through 30 September 2015). In addition, each of the above label requirements that contribute to the primary endpoint will be compared for the same two 1-year periods.

In addition:

1. The apparent indications, and the days supplied (≤7 days vs. >7 days) will be tabulated.
2. There will be a table showing the demographic characteristics, of the study population (sex, age group).

Milestones

Milestones	**Planned Date**
Start of data collection	Two months after protocol approval
End of data collection	When data through SEP2015 become available for analysis (estimated as 4Q2016)
<Registration in the EU PAS Register>	Before the start of the study
Final report of study results*	Twelve months after the end of data collection
*Timing of final report includes the following: Data analysis: Three months after data are available Final tables available: Two months after data analysis is complete Report writing: Three months Report review (full Consortium): Four months	

5. AMENDMENTS AND UPDATES

Amendment 1: 20JULY2016	
Abstract; 9.2.2. Study Period	**Changes:** Pre-implementation and post-implementation period dates have been clarified. **Rationale:** Provides more accurate dates of data collection, as requested by EMA.
3 Responsible Parties	**Change:** Principal/Coordinating Investigator has been added. **Rationale:** Investigator has been identified and is now included.
7.2 Background	**Change:** Dear Healthcare Professional Communication has been changed to Direct Healthcare Professional Communication. **Rationale:** Provides alignment with the definition in GVP Module XV
8.1 Primary Objectives	**Change:** Details provided for how the primary statistic, (a risk ratio comparing prescriptions' label compliance before vs. after the label change) will be calculated and reported. **Rationale:** Change made in response to EMA request for addition of a comparison between pre- and post-implementation period of risk minimisation measures
9.5 Study Size	**Change:** An estimate for the number of prescriptions available for study, and a table showing numbers of prescriptions required, have been added **Rationale:** Change made in response to EMA request for a sample size calculation.
9.7 Data Analysis	**Change:** Description of how the primary endpoint will be calculated has been edited to improve its clarity. **Rationale:** Change made in response to an EMA request to improve the readability of this part of the protocol.
Annex 1, Document 1 List of Companies	**Change:** Companies have been added, removed, and some company names have been changed. **Rationale:** Reflects companies that have joined and left the Consortium, as well as company name changes that have occurred.
Annex 2, ENCePP Checklist	**Change:** Page numbers updated **Rationale:** Changes to protocol resulted in changes to page numbers

6. MILESTONES

Milestones	Planned Date
Start of data collection	Two months after protocol approval
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Final report of study results*	Twelve months after the end of data collection
*Timing of final report includes the following: Data analysis: Three months after data are available Final tables available: Two months after data analysis is complete Report writing: Three months Report review (full Consortium): Four months	

7. RATIONALE AND BACKGROUND

7.1. Introduction

Domperidone, a gastrointestinal motility agent effective in the treatment of acute nausea and vomiting, was first approved in Belgium in March 1978. Currently, single-active-ingredient domperidone is licensed in more than 107 countries, including approximately 25 where it is sold without prescription. In the European Union, domperidone is registered in Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Slovak Republic, Slovenia, Spain, and the United Kingdom.

7.2. Background

In 2011, the EU Pharmacovigilance Working Party (PhVWP) recommended that the product information for domperidone-containing medicines should be updated to reflect the risk of adverse cardiac effects of domperidone including QT prolongation, arrhythmias, and sudden cardiac death, and that domperidone should be used with caution in patients with certain heart conditions, including heart failure, a previous heart attack, angina (chest pains), and heart rhythm disorders. In response to this recommendation, the SmPC was updated in 2012 to include QT prolongation as an adverse drug reaction (ADR).

In March 2013, the EMA PRAC initiated a review of domperidone-containing medicines at the request of the Federal Agency for Medicines and Health Products (FAMHP), under Article 31 of Directive 2001/83/EC over concerns about cardiac adverse effects of domperidone. Subsequently, PRAC recommended that the product label (Summary of Product Characteristics/SmPC and Patient Information Leaflet/PIL) of domperidone-containing medicines should be updated to strengthen the information regarding cardiac risks. In addition, PRAC raised concerns that there may be off-label use of domperidone for the stimulation of lactation in breastfeeding women, for the treatment of

gastro-oesophageal reflux disease (GERD), for the treatment of diabetic and non-diabetic gastroparesis, and for the treatment of symptoms of postural hypotension in Parkinson's patients. More recently the EMA asked that IBS be included in the present study as an off-label indication.

The recommended changes following conclusion of the Article 31 referral included the following:

- restriction of the indication to nausea and vomiting;
- limitation of duration of use to 7 days;
- reduction of the maximum daily dose to 10 mg TID for adults and adolescents (12 years of age and older and weighing 35 kg or more);
- reduction of the maximum daily dose to 0.25 mg/kg TID for neonates, infants, children (less than 12 years of age), and adolescents weighing less than 35 kg;
- contraindication of the combination with other drugs that increase the cardiac risks by themselves or increase the plasma level of domperidone; and
- contraindication in patients with moderate or severe hepatic impairment or certain cardiac conditions.

The CHMP continues to support a positive risk-benefit balance for domperidone provided that the drug is used according to the new label. Within the context of risk minimisation measures, the MAHs distributed a Direct Healthcare Professional Communication (DHPC), and updated the SmPC. PRAC requested that domperidone MAHs perform a drug utilisation study to assess the effectiveness of the above mentioned risk minimisation measures and to monitor the off-label use of the drug. In addition to a physician survey proposed by the MAHs to assess the prescribers' knowledge of the new label of domperidone, EMA suggested the use of a healthcare database as an additional data source to measure domperidone utilisation patterns. This protocol describes a drug utilisation study using healthcare databases in 5 European Union countries.

8. RESEARCH QUESTIONS & OBJECTIVES

The objective of the study is to investigate the effectiveness of risk minimisation measures and describe prescribing patterns of domperidone, including those pertaining to the off-label use of domperidone, in routine clinical practice in selected European Union countries.

8.1. Primary Objectives

To describe the prescribing patterns before and after the changes to the domperidone label and distribution of a DHPC and estimate and compare the overall proportion of domperidone prescriptions before and after implementation of the risk minimisation measures regarding the following measures:

- Composite endpoint consisting of the following components:
    - Maximum daily dose;
    - Duration of use (>7 days);
    - Concomitant medications that prolong the QT-interval or are potent or strong CYP3A4 inhibitors;
    - Prescribing to patients with contraindicated conditions, e.g., moderate or severe liver disease, underlying cardiac diseases; and
    - Prescribing for off-label indications

Domperidone is used as needed, therefore the duration of use may not be the same as the number of days for which domperidone is supplied. As a result, duration of use will be assessed under the following 2 scenarios, which will be likely to bracket the actual (but unknown) situation:

1. Domperidone is used only for as little as 1 dose after it is prescribed, and
2. Domperidone is used for the entire number of days supplied.

This is intended to bracket the plausible values for duration of use

Primary test statistic: In each country studied, the change in the proportion of all prescriptions that comply with the label based on the above composite endpoint during the 12 months before the label change versus the 12 months after the label change is the primary statistic to be evaluated as a measure of the effectiveness of the label change in that country. The statistic will be evaluated as a risk ratio, i.e., as the ratio of the proportion of prescriptions that met all conditions in the composite endpoint between 1 April 2013 and 31 March 2014 and the proportion of prescriptions that met all conditions in the composite endpoint between 1 October 2014 and 30 September 2015. The point estimate and 95% confidence interval for the above risk ratio will be reported. There are several versions of the composite endpoint that vary according to how the components of the composite endpoint are implemented in the databases and the risk ratio (point estimate and 95% confidence interval) will be reported for each. Note that the term “risk ratio” is being used in the sense of a ratio of probabilities (the probability of a prescription being consistent with the new label).

8.2. Secondary Objectives

To estimate the overall proportion of domperidone prescriptions before and after implementation of the risk minimisation measures for domperidone for each of the components of the composite endpoint individually, the time trend of apparent indication, and

days supplied (≤7 days vs. >7 days), and the age and sex of the people receiving prescriptions.

9. RESEARCH METHODS

9.1. Study Design

This is a post-authorisation, retrospective, observational cohort study using pre- and post-design to examine the changes in the prescribing patterns.

A cohort of patients prescribed domperidone will be identified from the following existing secondary data sources: CPRD for the United Kingdom and IMS databases for France, Germany, Belgium, and Spain. The countries are selected to include countries with relatively high per capita use of domperidone and at least 1 country with relatively low per capita use of domperidone as well as the availability of robust longitudinal electronic medical records databases in those countries. These data sources include information on prescriptions written, patient demographics, and diagnosis.

9.2. Setting and Study Population

9.2.1. Study Setting and Population

The study population will be defined as all patients receiving domperidone in the outpatient setting during the pre-defined periods (pre- and post- implementation periods of the risk minimisation activity) in the selected European Union countries (France, Germany, United Kingdom, Belgium, and Spain). Patients will be included in the study cohort if they have at least 1 prescription for domperidone in the selected databases during the pre-defined periods, and have membership or have been registered with the practice and have available medical history for at least 180 days before the domperidone prescription.

The date of the first prescription of domperidone in the pre-defined study periods will be defined as the index date. Patients will be followed from the index date to the earliest of the following dates:

- end of the study period;
- transfer out of the practice; or
- end of the practice's qualification as up to standard (a designation used in some databases to differentiate between practices that meet a data standard and those who do not for databases, such as CPRD).

9.2.2. Study Period

The study period will be divided into a background period and pre- and post- implementation periods of risk minimisation measures as follows:

- A background period (1 January 2011 through 31 March 2013)
- A 1-year pre-implementation period of risk minimisation measures (1 April 2013 through 31 March 2014)
- A 1-year post-implementation period of risk minimisation measures (1 October 2014 through 30 September 2015)

The period during which the label change took place and the DHPC was sent will be used as the period during which the risk minimisation measures were implemented (1 April 2014 through 30 September 2014).

Because the amendments to the product information were suggested by the PhVWP in October 2011, the study will track prescribing pattern changes from 1 January 2011 (a time that preceded most of the discussion and implementation of the label changes, i.e., a background period) through 30 September 2015.

9.3. Variables

9.3.1. Demographic Characteristics

Information on patients' age, sex, and geographic region will be extracted. Diagnoses will be extracted from a read codes (CPRD), ICD codes, or will be determined based on laboratory test results.

9.3.2. Indication

Indication will be estimated from the diagnoses recorded in the time period preceding each domperidone prescription:

- The indication for the prescription will be defined as nausea/vomiting if the subject has a recorded diagnosis classified as nausea or as vomiting, on the day of the prescription or in the preceding 7 days.
- For those prescriptions whose indication is not defined as nausea/vomiting, the indication will be defined as off-label if the subject has, in the 2 months up to and

including the date of domperidone prescription, a diagnosis classified as one of the following:

- GERD;
- Abdominal bloating, gastric dysmotility, delayed gastric emptying;
- IBS;
- Suppressed lactation, failed lactation, lactation not established, decreased lactation, lactation problem; or
- Orthostatic hypotension and a diagnosis of Parkinson's disease.

- For those prescriptions not classified as above, the indication will be classified as unknown.

For a list of the diagnostic terms and codes that will be used to identify the above conditions, see Annex 6.

9.3.3. Dose per Day

Dose per day will be described as dose in mg/day for subjects ≥12 years of age and in mg/kg/day for subjects <12 years of age (if weight information is available for up to 1 year prior to the prescription). Exceeding the maximum daily dose of 30 mg for adults and 0.25 mg/kg TID for children will be evaluated.

9.3.4. Use in Patients with Contraindicated Conditions

The contraindication for moderate or severe hepatic impairment will be identified by any diagnosis of hepatic cirrhosis, hepatic failure, or hepatic coma, between 1 January 2011 and 1 day before the prescription was written. The cardiac contraindication will be identified by a diagnosis of QTc prolongation, ventricular arrhythmia, or congestive heart failure in the 6 months before the prescription was written, or a diagnosis of hypokalemia in the 30 days before the prescription was written.

9.3.5. Concurrent Use with Drugs that Prolong the QT Interval or are Potent CYP3A4 Inhibitors

Domperidone is used as needed, therefore the duration of use may not be the same as the number of days for which domperidone is supplied. As a result, duration of use will be assessed under the following 2 scenarios, which will be likely to bracket the actual (but unknown) situation:

1. Domperidone is used only for as little as 1 dose after it is prescribed, and
2. Domperidone is used for the entire number of days supplied.

For the first scenario, the assessment of concurrent use with contraindicated medications will focus on drugs that were prescribed before or on the date of the domperidone prescription and whose duration of use includes the date of the domperidone prescription. For the second

scenario, assessment of concurrent use with contraindicated medications will also include drugs that were prescribed during the days' supply of the domperidone prescription.

A list of drugs that are known to prolong the QT interval is provided in Annex 3 and those that are potent or strong CYP3A4 inhibitors appear in Annex 4.

9.3.6. A Composite Endpoint -All Label Requirements

Each prescription will be classified according to whether it appears to violate at least 1 of the above specifications, i.e., has a presumed indication that is off-label, has a dose that is above 30 mg/day (for ages ≥12 years) or above 0.75 mg/kg/day (for ages <12 years), is written for a patient with a contraindicated condition, or appears to be prescribed concurrently with a medication contraindicated for concurrent use.

To accommodate the 2 areas of uncertainty described above (1] duration of domperidone use and 2] domperidone prescriptions for which the indication is unknown), the above classification will be done in the following 4 ways to reflect the possible combinations of:

- With consideration of days' supply being more than 7 days;
- Without consideration of days' supply being more than 7 days;
- With classifying subjects with an unknown indication as having an off-label indication; and
- Without classifying subjects with an unknown indication as having an off-label indication

This is described in more detail in Section 9.7.

9.3.7. Length of Treatment

The duration of each prescription will be estimated from the days' supply, if available or will be calculated directly as the total prescription quantity divided by daily number of pills recommended in the dosing instructions. However, because domperidone may be used as needed (i.e., pro re nata [PRN]), the number of days supplied may not be a reliable measure for the actual length of treatment. Therefore, compliance with the label will be estimated with and without a requirement that the days' supply will be no more than 7 days.

9.4. Data Sources

Patient information on domperidone exposure and study endpoints will be obtained from existing data sources. In order to meet the study objectives, the following data sources will be considered:

Longitudinal Electronic Medical Records (EMR) Databases:

- IMS longitudinal patient databases providing systematic ongoing information from physician office-based visits on patients' consultations, diagnoses and treatment in Germany, France, Belgium, and Spain.
- CPRD: a longitudinal anonymised electronic medical records (EMRs) database containing detailed information on symptoms, diagnoses, prescriptions, investigations, and hospital referrals, as well as basic demographics. Longitudinal data are collected for a sample of over five million active patients registered with over 650 general practices throughout the United Kingdom.

These data sources and countries are subject to change depending on data availability. For additional details on the electronic databases, see Annex 5.

9.5. Study Size

The study size will vary according to country and data source. All patients available in the study population will be considered for the analysis. Preliminary estimates indicate that the suggested databases capture at least several thousands of domperidone prescriptions in each of the countries being studied.

Review of domperidone sales data for 2015 from IMS and from the CPRD indicates that the number of prescriptions in each of the databases varies by country. The lowest number of prescriptions was observed in the Belgian database, where the count was 22,000.

Table 2 shows the approximate number of prescriptions for a study with the same number of prescriptions in pre-intervention period and the post-intervention to have 90% power to detect, $p<0.05$ (2-sided test) risk ratios from 1.1 to 1.4 according to the risk during the pre-intervention period. Note that the "risks" are the probabilities of a prescription meeting the label requirements, so a risk ratio of 1.1 represents a 10% improvement in label compliance when comparing the post-intervention period to the pre-intervention period.

Table 2: Approximate number of Subjects Required per Group (Before Intervention, After Intervention) Under Various Scenarios				
"Risk" of complying with label before the intervention period	"Risk" Ratio = 1.1	"Risk" Ratio = 1.2	"Risk" Ratio = 1.3	"Risk" Ratio = 1.4
10%	16,000	4,500	2,000	1,200
20%	7,200	1,800	900	500
30%	4,000	1,100	500	300
40%	2,700	700	300	200
50%	1700	500	200	100
60%	1200	300	200	100
70%	700	200	100	100
80%	400	100	100	100

Thus, if compliance with the new label requirements as low as 10% in the pre-intervention period, the study will have ≥90% power to detect even a risk ratio of 1.1 (a 10% improvement), and smaller improvements would be of limited public health interest. If compliance with the new label is higher than 10% in the pre-intervention period, the study will have ≥90% power to detect smaller improvements in compliance with the new label. All domperidone prescriptions that are captured during the study period and meet the inclusion criteria will be included in data analysis.

9.6. Data Management

The study will use existing databases with anonymized information on the individual patients. The processes for database management differ by the data source. Data extraction and analysis will be performed according to the standard practices of the data suppliers.

9.7. Data Analysis

Data analysis in the study will be descriptive. Continuous variables will be presented using appropriate descriptive statistics, such as mean, median, standard deviation and range. Categorical variables will be presented using percent and frequency tables. The rates and 95% CI of all study endpoints (i.e., risk minimisation indicators) will be calculated for the 2011-2015 period, using quarterly time blocks for the pre- and post- risk minimisation implementation periods. The rates will be calculated per 1000 domperidone-treated patients or as percentage of domperidone prescriptions, as appropriate. Paediatric data will be described separately from adult patients and rate of paediatric use will be calculated as fraction of overall domperidone utilisation. Missing values will be reported as missing and no imputation will be undertaken. All data analysis will be done in SAS using the version that is current when the analyses are done.

The rates for the primary endpoints of the study (the proportion of all prescriptions that are consistent with the revised label) will be calculated 4 ways to address uncertainty about 1) Unknown indication (is it assumed to be nausea and vomiting and therefore on-label, or is it assumed to be some other indication and therefore off-label) and 2) Duration of use that may be shorter than the days' supply (prescriptions with more than 7 days' supply assumed to

be intended for ≤7 days use, and provision of additional tablets for possible future episodes, and therefore on-label, versus assumed to be for >7 days use and therefore off –label):

1. Unknown indication assumed to be nausea and vomiting. Duration assumed to be ≤7 days (most optimistic scenario) meets the following conditions:

    a. Prescription for nausea and vomiting or unknown indication but no recent diagnosis of GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson patients, or as an aid to lactation;

    b. Dose no higher than recommended;

    c. No prescription to patients with certain cardiac and hepatic conditions; and

    d. No co-prescription with CYP3A4 inhibitors or QT-prolonging drugs. (This considers such contraindicated co-medications only when they were prescribed ≤ the date of the domperidone prescription.)

2. Unknown indication assumed to be an off-label indication, duration assumed to be ≤7days (an intermediate scenario) meets the following conditions:

    a. Prescription for nausea and vomiting but no recent diagnosis of GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson patients, or as an aid to lactation. Unknown indication will be assumed to be off-label (This differs from #1 above);

    b. Dose no higher than recommended;

    c. No prescription to patients with certain cardiac and hepatic conditions; and

    d. No co-prescription with CYP3A4 inhibitors or QT-prolonging drugs (This considers such contraindicated co-medications only when they were prescribed ≤ the date of the domperidone prescription)

3. Unknown indication assumed to be nausea and vomiting, duration assumed to be the days' supply (an intermediate scenario) meets the following conditions:

    a. Prescription for nausea and vomiting or for unknown indication but no recent diagnosis of GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson patients, or as an aid to lactation (This is the same as in #1 above);

    b. Duration (days' supply) ≤7 (This differs from #1 above and from #2 above, which don't examine days' supply)

    c. Dose no higher than recommended;

    d. No prescription to patients with certain cardiac and hepatic conditions; and

e. No co-prescription with CYP3A4 inhibitors or QT-prolonging drugs. (Considers such contraindicated co-medications when prescribed ≤ the date of the domperidone prescription or prescribed within the days potentially covered by the domperidone prescription).

4. Unknown indication assumed to be an off-label indication, duration assumed to be the days' supply (most pessimistic scenario)

    a. Prescription for nausea and vomiting but no recent diagnosis of GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson patients or as an aid to lactation; Unknown indication assumed to be off-label (This differs from #1 above)

    b. Duration (days' supply) ≤7 (This differs from #1 above and from #2 above, which don't examine days' supply.)

    c. Dose no higher than recommended;

    d. No prescription to patients with certain cardiac and hepatic conditions; and

    e. No co-prescription with CYP3A4 inhibitors or QT-prolonging drugs. (Considers such contraindicated co-medications when prescribed ≤ the date of the domperidone prescription or prescribed within the days potentially covered by the domperidone prescription).

Rates of the study endpoints will be assessed for the pre-implementation period (1 April2013 through 31 March2014) and will be compared with the 1-year post-implementation period (1 October2014 through 31 March2015). In addition, each of the above label requirements that contribute to the primary endpoint will be compared for the same two 1-year periods.

In addition:

1. The apparent indications, and the days supplied (≤7 days vs. >7 days) will be tabulated.

2. There will be a table showing the demographic characteristics, of the study population (sex, age group).

9.8. Quality Control

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits of the data, consistency of collected data, validation of coding, 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. Written programming will be reviewed independently. All key study documents, such as the statistical analysis plan and study reports, will undergo quality control and senior scientific review.

The study will be executed in line with all applicable regulations and guidelines, such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology as well as the data vendor's quality management system.

9.9. Limitations of the Research Methods

9.9.1. Strengths

- The study will use longitudinal real-life data on the utilisation of domperidone in different European countries with a pre- and post- study design to measure the effectiveness of the risk minimisation activities and examine changes on prescribing patterns. Data on prescription patterns prior to the label change provide a useful comparator for the prescription patterns observed after the label change.

- The data from this study are not collected by specific consent of patients or prescribers and thus are not subject to volunteer and reporting bias.

- All prescriptions for eligible patients that are captured by the database will be included, providing a robust sample size and a statistically-reliable estimate of compliance with the new domperidone label.

- Data on prescription patterns prior to the label change provide a useful comparator for the prescription patterns observed after the label change and distribution of the DHPC. Thus this study provides an opportunity to demonstrate not only the final outcomes of the implemented risk minimisation measures, but also to demonstrate the effectiveness of the implementation process by comparing the endpoints "before" and "after" the implementation.

- Using the combination of the prescribers' survey and healthcare database analysis, the extent of domperidone on-label vs. off-label prescription will be assessed both in terms of process indicators (investigated through survey) and outcome indicators (investigated through database analysis). This should provide a comprehensive view of the effectiveness of domperidone risk minimisation measures.

9.9.2. Limitations

- The databases provide detailed information on prescribed and/or dispensed medications but not on the actual use of the medications by patients. This may

specifically be a limitation for drug that are used PRN, such as domperidone. Thus, patients may be classified as exposed when they are not actually taking the drug.

- The databases often do not record the intended duration of use of each prescription (days of supply). This can result in misclassification of drug exposure.

- Because domperidone is used as needed, missing information about the true length of treatment is likely to be an important source of uncertainty in estimating compliance with the recommendation to limit use to ≤7 days, and may also be an important source of uncertainty about the frequency with which domperidone is used concurrently with a contraindicated medication that was prescribed after domperidone was prescribed.

- In these databases prescriptions are not explicitly linked to diagnoses. The indication for which the drug is prescribed is deduced from the list of diagnoses documented in patient's records on or shortly before the day of the prescription. If a substantial proportion of prescriptions do not have a diagnosis that is plausible as an indication, this study is likely to leave appreciable uncertainty about the indications for which the medication is prescribed. Attempts to obtain this missing information from chart review or questionnaires would be subject to volunteer bias and there is no guarantee that the missing information on indication would be recorded in a high proportion of the charts that were made available.

- The databases do not include a unique patient identifier that would make it possible to identify as a single individual a patient who is attending multiple physicians. Therefore some diagnoses that contraindicate domperidone use, and some domperidone use that is concurrent with contraindicated medications, will be missed in this study.

9.10. Other Aspects

None

10. PROTECTION OF HUMAN SUBJECTS

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

The study is a post-authorisation safety study (PASS) and will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC (European Commission, 2008) and the 2012 Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies (EMA, 2012a, module VIII). The study will comply with the nature of non-interventional (observational) studies referred to in the ICH harmonised tripartite guideline Pharmacovigilance Planning E2E (ICH, 2004).

All data used in the study will be anonymised and analysis will be performed on a de-identified patient-level dataset. Since electronic records will be anonymised, written informed consent is not required. The data system will be maintained and secured as requested by the local patient privacy regulations of each country participating in the study. Processes assuring data security will be employed during data extraction, storage and back-up. The data and all study documents will be kept until MAH's written notification that records may be destroyed.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND ADVERSE REACTIONS

Throughout the conduct of the study the vendor will be responsible for collecting and reporting adverse events to the sponsor (Janssen Research & Development on behalf of the Consortium). In instances where individual patient data review identifies adverse events, serious adverse events, or special situations that may be attributable to domperidone, the events will be reported as individual case safety reports (ICSR) to the sponsor under expedited timelines as appropriate per company Standard Operating Procedures (SOPs). All adverse events collected throughout the study, both aggregate findings and individual reports, will be summarised in the study report. Data collected on other products not included in the programme/protocol design must also be collected and reported as spontaneous ICSR but may not be included in the study report. If the vendor is unable to evaluate if the ICSR meets criteria or if unclear if the ICSR must be forwarded to the sponsor, the ICSR must be forwarded to the sponsor for final determination. Each Consortium member will follow their company SOPs with regard to the reporting of adverse events as ICSRs.

Adverse events and special situations considered as endpoints per Section 9.3.6 A Composite Endpoint -All Label Requirements will not be forwarded to the sponsor.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Common study protocol, study status, and report(s) will be included in regulatory communications in line with the risk management plan, Periodic Safety Update Report (PSUR), and other regulatory milestones and requirements. Study results will be considered for publication and will follow the International Committee of Medical Journal Editors (ICMJE, 2010) guidelines. In addition, communication in appropriate scientific meetings will be considered.

When reporting results of this study, the appropriate STROBE checklist (STROBE, 2007) will be followed.

13. REFERENCES

1. Matcho A, Ryan P, Fife D, Reich C. Fidelity Assessment of a Clinical Research Practice Datalink Conversion to the OMOP Common Data Model. Drug Safety 2014;37(11):945-959.

ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

Number	Date	Title
1	9FEB2015	List of Companies Participating in the Domperidone Collaboration Study Group

Document Number 1: List of Companies Participating in the Domperidone Collaboration Study Group		
Parent Company	**MAH**	**MAH Address**
Johnson & Johnson	Janssen-Cilag Pharma Gmbh	Vorgartenstraße 206B, AT-1020 Vienna Austria
Johnson & Johnson	Johnson & Johnson Consumer NV/SA	Antwerpseweg 15-17, 2340, Beerse, Belgium
Johnson & Johnson	Johnson & Johnson, Prodaja Medicinskih In Farmacevtskih Izdelkov, D.O.O.	Smartinska cesta 53, SI-1000, Ljubliana, Slovenia
Johnson & Johnson	Janssen-Cilag International NV	Turnhoutseweg 30, 2340, Beerse, Belgium
Johnson & Johnson	Janssen-Cilag s.r.o.	Karla Engliše 3201/6, 150 00 Prague 5
Johnson & Johnson	Janssen-Cilag A/S	Hammerbakken 19, DK-3460 Birkerød, Denmark
Johnson & Johnson	Janssen-Cilag S.A.	Paseo de las Doce Estrellas, 5-7, 28042 Madrid, Spain
Johnson & Johnson	Janssen-Cilag	1, rue Camille Desmoulins, TSA 91003, 92787 Issy Les Moulineaux, Cedex 9, France
Johnson & Johnson	Johnson & Johnson Hellas Consumer AE	Aegialias & Epidavrou 4, 15125, Maroussi, Athens, Greece
Johnson & Johnson	Janssen-Cilag Kft.	H-2045, Törökbálint, To Park, Hungary
Johnson & Johnson	McNeil Healthcare (Ire) Ltd	Airton Road, Tallaght, Dublin 24, Ireland
Johnson & Johnson	Janssen-Cilag Spa	Via M.Buonarroti, 23, I-20093 Cologno Monzese, Italy
Johnson & Johnson	UAB „Johnson & Johnson“	Geležinio Vilko g. 18A, LT-08104 Vilnius, Republic of Lithuania
Johnson & Johnson	Johnson & Johnson Consumer NV/SA	Antwerpseweg 15-17, 2340, Beerse, Belgium
Johnson & Johnson	Johnson & Johnson Consumer B.V.	Roosveltweg 15, 1314 SJ Almere
Johnson & Johnson	Johnson & Johnson s.r.o	Karadžičova 12, 821 08 Bratislava, Slovak Republic
Johnson & Johnson	Johnson & Johnson, Lda.	Estrada Consiglieri Pedroso, 69 A - Quelez de Baixo, 2730-055 Barcaerna, Portugal
ABC Farmaceutici	ABC Farmaceutici S.p.A.	Corso Vittorio Emanuele II, 72 – 10121 – Turin, Italy
Actavis Group PTC	Actavis Group PTC ehf.	Reykjavikurvegur 76-78 - 220 Hafnarfjördur - Iceland
Angenerico	Acraf S.p.A.	Viale Amelia 70 – 00181 Rome – Italy
Aurobindo Pharma	Aurobindo BV	Baarnsche Dijk 1, 3741 LN Baarn – The Netherlands
Aurobindo Pharma	Alternova A/S	Lodshusvej 11, 4230 Skælskør, Denmark
Aurobindo Pharma	Arrow Génériques SAS	26 Av. Tony Garnier – 69007 Lyon – France
Aurobindo Pharma	Aurovitas Unipessoal Lda	Avenida do Forte, No 3, Parque Suecia, Edificio IV, 2º, 2794-038, Carnaxide,- Portugal
Aurobindo Pharma	Milpharm Ltd	Ares Block, Odyssey Business Park, West End Road, South Ruislip – Middlesex

Document Number 1: List of Companies Participating in the Domperidone Collaboration Study Group		
Parent Company	**MAH**	**MAH Address**
		HA4 6QD – United Kingdom
Aurobindo Pharma	Aurex	Baarnsche Dijk 1, 3741 LN Baarn – The Netherlands
Aurobindo Pharma	Sofar SpA	Via Firenze 40, 20060 Trezzano Rosa (MI) - Italy
Aventis Pharma Ltd.	Sanofi-Aventis France	82 avenue Raspail, 94 250 Gentilly – France
Aventis Pharma Ltd.	Winthrop Pharmaceuticals UK Limited	One Onslow Street, Guildford - Surrey GU1 4YS - United Kingdom
Azevedos	Laboratórios Azevedos – Indústria Farmacêutica SA	Estrada Nacional 117-2, Edificio Azevedos, Alfragide – 2614-503 Amadora – Portugal
Betapharm Arzneimittel	Betapharm Arzneimittel GmbH	Kobelweg 95 - 86156 Augsburg – Germany
Biogaran	Biogaran	15 Boulevard Charles de Gaulle - 92707 Colombes Cedex - France
Bristol Laboratories	Bristol Laboratories Limited	Unit 3, Canalside Northbridge Road – Berkhamsted, Hertfordshire HP4 1EG - United Kingdom
Co-Pharma	Co-Pharma Ltd	Unit 4, Metro Centre, Tolpits Lane – Watford, Herts – WD18 9SS – United Kingdom
DOC Generici	DOC Generici Srl	Via Turati 40 – 20121 Milan – Italy
Esteve	Laboratorios del Dr. Esteve SA	Av. Mare de Deu de Montserrat 221 – 08041 Barcelona – Spain
Focus Pharmaceuticals	Focus Pharmaceuticals Ltd.	Unit 5 Faraday Court, First Avenue, Centrum 100 – Burton upon Trent, Staffordshire, DE14 2WX – United Kingdom
Generis Farmacêutica	Generis Farmacêutica SA	Rua João de Deus, 19 - 2700-487 Amadora - Portugal
Giuliani Pharma	Giuliani SpA	Via Palagi 2 – 20129 Milan – Italy
Hexal	Hexal AG	Industriestr. 25 - 83607 Holzkirchen – Germany
Hexal	1 A Pharma GmbH	Keltenring 1 + 3 – 82041 Oberhaching – Germany
Hexal	Rowex Ltd	Bantry, Co. Cork – Ireland
Hexal	Sandoz S.A.S.	49 avenue Georges Pompidou - 92593 Levallois-Perret Cedex, France
Hexal	SANDOZ SpA	Largo Umberto Boccioni 1 - 21040 Origgio – Varese – Italy
Hexal	Sandoz BV	Veluwezoom 22 -1327 AH Almere - The Netherlands
Italchimici	Italchimici S.p.A.	Via Pontina 5, km 29 - 00071 Pomezia (RM) – Italy
Kela Pharma	Kela Pharma NV	Industriepark West 68 – 9100 Sint-Niklaas – Belgium
Labesfal Genéricos	Labesfal Genéricos SA	Av. Dr. Afonso Costa, n° 1370 – 3465-051 Campos de Besteiros – Portugal
Laboratoire Gerda	Gerda Laboratoires SAS	24 rue Erlanger – 75016 Paris – France

Document Number 1: List of Companies Participating in the Domperidone Collaboration Study Group		
Parent Company	**MAH**	**MAH Address**
Laboratório Medinfar – Produtos Farmacêuticos	GP - Genéricos Portugueses, Lda.	Rua Henrique de Paiva Couceiro, 29 Venda Nova - 2700-451 Amadora – Portugal
Laboratório Medinfar – Produtos Farmacêuticos	Laboratório Medinfar - Produtos Farmacêuticos, S.A.	Rua Manuel Ribeiro de Pavia, 1 - 1º, Venda Nova - 2700-547 Amadora – Portugal
Manx Healthcare	Manx Healthcare Limited	Taylor Group House, Wedgnock Lane - Warwick CV34 5YA – United Kingdom
MEDA (Rottapharm)	MEDA Pharma S.L. (Rottapharm S.L.)	Av. Castilla 2 (Edif. Berlin 2ª Pl) - 28830 San Fernando de Henares – Spain
Mylan EMEA	Mylan SPRL	Park Rozendal, Terhulpsesteenweg 6A – 1560 Hoeilaart – Belgium
Mylan EMEA	Mylan SAS	117 Allée des Parcs – F 69792 Saint-Priest Cedex – France
Mylan EMEA	Mylan SpA	Via Vittor Pisani 20 – 20124 Milan – Italy
Mylan EMEA	Mylan BV	Dieselweg 25 – NL-3752 LB Bunschoten – The Netherlands
Mylan EMEA	Mylan Lda	Parque Expo, Edifício Atlantis, Avenida D. João II, Lote 1.06.2.2 C - 7.3 e 7.4 - 1990-095 Lisbon – Portugal
Pensa Pharma	Pensa Pharma SpA	Via Ippolito Rosellini 12 – 20124 – Milan - Italy
Pensa Pharma	Pensa Pharma SA	C/ Jorge Comín (médico pediatra) 3 - 46015 Valencia– Spain
Pensa Pharma	TOLIFE Produtos Farmacêuticos S.A.	Avenida do Forte nº 3, Edifício Suécia IV, Piso 0 - 2794-093 Carnaxide - Portugal
Pierre Fabre	Pierre Fabre Médicament SAS	45 place Abel Gance – 92100 Boulogne – France
Pierre Fabre	Pierre Fabre Farmaka AE	Mesogeion AV 350, Agia Paraskevi – 15341 Athens - Greece
Pierre Fabre	Pierre Fabre Pharma Srl	Via Winckelmann 1 - 20146 Milan - Italy
S.F. Group	S.F. Group Srl	Via Tiburtina 1143 – 00156 - Rome - Italy
STADA	ALIUD PHARMA GmbH - Laichingen	Laichingen, Germany
STADA	Centrafarm BV	Nieuwe Donk 3 - 4879 AC Etten-Leur - The Netherlands
STADA	Ciclum Farma Unipessoal Lda	Paco de Arcos - Portugal
STADA	Crinos SpA	Milan - Italy
STADA	EG SpA	Milan - Italy
STADA	EG LABO Laboratoires EuroGenerics	Boulogne-Billancourt Cedex - France
STADA	Eurogenerics NV/SA	Brussels - Belgium
STADA	Healthypharm BV	Etten-Leur - Netherlands
STADA	Stada Arzneimittel AG	Stadastrasse 2-18 - 61118 Bad Vilbel – Germany
STADA	STADApharm GmbH	Stadastr. 2-18 - 61118 Bad Vilbel – Germany

Document Number 1: List of Companies Participating in the Domperidone Collaboration Study Group		
Parent Company	**MAH**	**MAH Address**
Sun Pharmaceuticals Industries Ltd	Terapia SA	Str. Fabricii nr. 124 - Cluj Napoca - Romania
Takeda	Takeda GmbH	Byk-Gulden-Str. 2 - 78403 Konstanz - Germany
Teva	AbZ-Pharma GmbH	Graf-Arco-Str. 3 - 89079 Ulm - Germany
Teva	Mediq Farma B.V	Hertogswetering 159 - 3543 AS Utrecht - The Netherlands
Teva	Pharmachemie BV	Swensweg 5 - Haarlem 2031 GA - The Netherlands
Teva	Ratiopharm GmbH	Graf-Arco-Str. 3 - 89079 Ulm - Germany
Teva	Ratiopharm Lda	Lagoas Park, Edifício 5 A, Piso 2 - 2740-245 Porto Salvo – Portugal
Teva	Teva Pharma Belgium NV	Laarstraat 16 - 2610 Wilrijk – Belgium
Teva	Teva GmbH	Graf-Arco-Str. 3 - 89079 Ulm - Germany
Teva	Teva Italia Srl	Via Messina, 38 - 20154 Milan – Italy
Teva	Teva Nederland BV	Swensweg 5 - Haarlem 2031 GA - The Netherlands
Teva	Teva Pharmaceuticals Europe BV	Piet Heinkade 107 - 1019 GM Amsterdam - The Netherlands
Teva	Teva Santé SAS	100-110 Esplanade du General de Gaulle - 92931 La Defense Cedex - France
Wockhardt Limited	Wockhardt UK Limited	Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF, United Kingdom
ZYDUS France	ZYDUS France SAS	ZAC des Hautes Pâtures, 25, rue des Peupliers, Bât. L – 92752 Nanterre Cedex - France

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

A Drug Utilisation Study of Domperidone in Europe Using Databases

Study reference number:

To be determined

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[a]	☒	☐	☐	9,11
1.1.2 End of data collection[b]	☒	☐	☐	9,11
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	9,11
1.1.6 Final report of study results.	☒	☐	☐	9,11

Comments:

Progress or interim reports are not required as the final study report is planned to be submitted shortly after the end of data collection.

[a] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7,12,13
2.1.2 The objective(s) of the study?	☒	☐	☐	7,12-14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7,12,14
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This study examines drug utilisation. Due to the descriptive nature of the study no formal hypothesis is tested.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	7,14
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	7,8,13,14
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	8,13,19-21

Comments:

This is a drug utilisation study examining the extent and patterns of drug use. Due to the descriptive nature of the study measure of effect will not be described

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	7,8.14
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	8,15
4.2.2 Age and sex?	☒	☐	☐	8,13
4.2.3 Country of origin?	☒	☐	☐	7,14
4.2.4 Disease/indication?	☒	☐	☐	15,16
4.2.5 Co-morbidity?	☒	☐	☐	15.16
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	14

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	14-17
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	22,23
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

This is a drug utilisation study examining the extent and patterns of drug use. Classification of exposure is not relevant to the study's objectives.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	8,9,15-17
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	17-18, 22,23

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

This is a drug utilisation study examining the extent and patterns of drug use. Therefore, confounders and effect modifiers are not applicable.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	8,15-17
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☒	8,16,17
8.1.3 Covariates?	☒	☐	☐	8,14,17
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	16,17
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8,16,17
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	8,14,17
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	15,39-43
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	15,39-43
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

This is a drug utilisation study examining the extent and patterns of drug use. Data on drug utilization will be available within the data source. No additional linkage will be required. The coding system will depend on the data source used and will be de

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	18,19

Comments:

Sample size is provided for one of the data source to be used in the study. This is a drug utilisation study examining the extent and patterns of drug use. Due to the descriptive nature of the study statistical power was not calculated.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	16,17
10.3 Are descriptive analyses included?	☒	☐	☐	19,21
10.4 Are stratified analyses included?	☒	☐	☐	7,14
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

This is a drug utilisation study examining the extent and patterns of drug use. Therefore, the analysis planned for the study is descriptive in nature. Results are stratified by country.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	21,22
11.3 Are methods of quality assurance described?	☒	☐	☐	21,22
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	22,23
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	22,23
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	18,19
12.3 Does the protocol address other limitations?	☒	☐	☐	23

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

The study utilise secondary databases and therefore ethics committee approval will not be required. The study will comply with the relevant guideless as specified in Section 9

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	10

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	24
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	24

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

ANNEX 3: LIST OF DRUGS WITH A KNOWN RISK OF TORSADES DE POINTES*

Amiodarone	Dofetilide	Methadone
Anagrelide	Domperidone[b]	Moxifloxacin
Arsenic trioxide	Donepezil	Ondansetron
Astemizole[a]	Dronedarone	Pentamidine
Azithromycin	Droperidol	Pimoside
Bepridil[a]	Erythromycin	Probucol[a]
Chloroquine	Escitalopram	Procainamide[d]
Chlorpromazine	Flecainide	Propofol
Cilostazol	Fluconazole	Quinidine
Ciprofloxacin	Grepafloxacin[c]	Sevoflurane
Cisapride[a]	Halofantrine	Sotalol
Citalopram	Haloperidol	Sparfloxacin[a]
Clarithromycin	Ibutilide	Sulpiride[b]
Cocaine	Levofloxacin	Terfenadine[a]
Disopyramide	Levomethadyl[a]	Thioridazine
	Mesoridazine[a]	Vandetanib

[a] Removed from US market
[b] On non-US market
[c] Off-market worldwide
[d] Oral off US market

*Taken from Credible Meds Filtered QTDrug List (revised 4MAY2015)

ANNEX 4: LIST OF STRONG IN VIVO INHIBITORS OF CYP3A ENZYMES#

Strong CYP3A inhibitors (≥5-fold increase in AUC or >80% decrease in CL)

Boceprevir
Clarithromycin
Conivaptan
Grapefruit juice[a]
Indinavir
Itraconazole
Ketoconazole
Lopinavir/Ritonavir
Mibefradil[b]
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Voriconzole

[a] The effect of grapefruit juice varies widely among brands and is concentration-, dose- and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high-dose, double-strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low-dose, single-strength)

[b] Withdrawn from the United States market

#Referenced from FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for dosing, and Labeling Recommendations (pages 41 through 43) and the CHMP 2012 Guideline on the Investigation of Drug Interactions (page 48).

ANNEX 5: DESCRIPTION OF DATABASES

CPRD

The Clinical Practice Research Datalink (CPRD) consists of anonymized electronic health records from primary care practices in the UK from 1987 to the present. It includes diagnoses (by Read codes), signs and symptoms, procedures, laboratory values, lifestyle factors, clinical and administrative/social data, and prescriptions written (not dispensed). It is considered broadly representative of the general UK population in terms of age, sex, and geographic distributions (~8% of the UK population). The validity of the CPRD has been extensively studied, demonstrating good agreement between the electronic medical records and capture of information from specialists and prescriptions. Data are updated monthly (e.g., December 2015 data is available by the end of January 2016).

LPD (France)

The Longitudinal Practice Database (LPD) consists of anonymized patient records collected from patient management software used by General Practitioners (GPs) and select specialists (diabetology, gastroenterology, cardiology, pneumology, rheumatology, gynecology, neurology, and psychiatry) during office visits to document patients' clinical records from 1994 to the present. Data are updated monthly and there are 1.8 million active patients. It includes patient demographics, comorbidities, diagnoses (by ICD-10 codes), signs and symptoms, laboratory values, and prescriptions written (not dispensed).

Disease Analyzer (Germany)

The Disease Analyzer consists of anonymized patient records collected from patient management software used by GPs and select specialists (diabetology, gastroenterology, cardiology, nephrology, pneumology, rheumatology, surgery, dermatology, gynecology, ENT, neurology, psychiatry, orthopaedics, pediatrics, and urology) within their practice, clinic, or hospital during an office visit to document patients' clinical records from 1992 to the present. Data are updated approximately every six weeks (e.g., data for December 2015 is available at the end of February 2016). It includes patient demographics, comorbidities, diagnoses (by ICD-10 codes), signs & symptoms, risk factors, laboratory values, prescribed drug therapy, and hospitalizations.

LPD (Spain)

The LPD in Spain consists of anonymized patient records collected from patient management software used by GPs and select specialists (gastroenterology, cardiology, pneumology, rheumatology, gynecology, neurology, psychiatry, urology, endocrinology, internal medicine, ophthalmology, nephrology, trauma, pediatrics, and dermatology) during an office visit to document patients' clinical records from 2011 to the present (data collection from GPs began in 2011; data collection from specialists began in 2012) and is updated monthly. It includes patient demographics, comorbidities, diagnoses (by ICD-9-CM codes), symptoms, laboratory values, and prescriptions written (not dispensed).

LPD (Belgium)

The LPD in Belgium consists of anonymized patient records collected from patient management software used by GPs during an office visit to document patients' clinical records from 2005 to the present. Data are updated monthly and data for a study period are usually available within three weeks after the end of the study period. For example, for a study period ending December 2015, data are usually available by the end of January 2016. There are 370,000 active patients in the database. It includes patient demographics, comorbidities, diagnoses (by ICD-10 codes), symptoms, laboratory values, and prescriptions written (not dispensed).

ANNEX 6: VARIABLES TO BE USED IN DATABASES

Condition	ICD-9 Codes	Text
Abdominal Bloating	536.3	Gastroparesis
GERD	530.11	Reflux esophagitis
GERD	787.1	Heartburn
GERD	787.2	Dysphagia
GERD	787.20	Dysphagia, unspecified
GERD	787.21	Dysphagia, oral phase
GERD	787.22	Dysphagia, oropharyngeal phase
GERD	787.23	Dysphagia, pharyngeal phase
GERD	787.24	Dysphagia, pharyngoesophageal phase
GERD	787.29	Other dysphagia
IBS	555	Regional enteritis
IBS	555.0	Regional enteritis of small intestine
IBS	555.1	Regional enteritis of large intestine
IBS	555.2	Regional enteritis of small intestine with large intestine
IBS	555.9	Regional enteritis of unspecified site
IBS	556	Ulcerative colitis
IBS	556.1	Ulcerative (chronic) ileocolitis
IBS	556.3	Ulcerative (chronic) proctosigmoiditis
IBS	556.5	Left-sided ulcerative (chronic) colitis
IBS	556.6	Universal ulcerative (chronic) colitis
IBS	556.8	Other ulcerative colitis
IBS	556.9	Ulcerative colitis, unspecified
Nausea and Vomiting	78.82	Epidemic vomiting syndrome
Nausea and Vomiting	536.2	Persistent vomiting
Nausea and Vomiting	564.3	Vomiting following gastrointestinal surgery
Nausea and Vomiting	643	Excessive vomiting in pregnancy

Condition	ICD-9 Codes	Text
Nausea and Vomiting	643.2	Late vomiting of pregnancy, unspecified as to episode of care or not applicable
Nausea and Vomiting	643.2	Late vomiting of pregnancy
Nausea and Vomiting	643.21	Late vomiting of pregnancy, delivered, with or without mention of antepartum condition
Nausea and Vomiting	643.23	Late vomiting of pregnancy, antepartum condition or complication
Nausea and Vomiting	643.8	Other vomiting complicating pregnancy
Nausea and Vomiting	643.8	Other vomiting complicating pregnancy, unspecified as to episode of care or not applicable
Nausea and Vomiting	643.81	Other vomiting complicating pregnancy, delivered, with or without mention of antepartum condition
Nausea and Vomiting	643.83	Other vomiting complicating pregnancy, antepartum condition or complication
Nausea and Vomiting	643.9	Unspecified vomiting of pregnancy
Nausea and Vomiting	643.9	Unspecified vomiting of pregnancy, unspecified as to episode of care or not applicable
Nausea and Vomiting	643.91	Unspecified vomiting of pregnancy, delivered, with or without mention of antepartum condition
Nausea and Vomiting	643.93	Unspecified vomiting of pregnancy, antepartum condition or complication
Nausea and Vomiting	787.03	Vomiting alone
Nausea and Vomiting	787.0	Nausea and vomiting
Nausea and Vomiting	787.01	Nausea with vomiting
Nausea and Vomiting	787.02	Nausea alone
Orthostatic Hypotension	458.0	Orthostatic hypotension
Orthostatic Hypotension	780.2	Syncope and collapse
Orthostatic Hypotension	992.1	Heat syncope
Parkinson's	094.82	Syphilitic parkinsonism
Parkinson's	332	Parkinson's disease
Parkinson's	332.0	Paralysis agitans
Parkinson's	332.1	Secondary parkinsonism
Suppressed Lactation	676	Other disorders of the breast associated with childbirth and disorders of lactation
Suppressed Lactation	676.4	Failure of lactation
Suppressed Lactation	676.40	Failure of lactation, unspecified as to episode of care or not applicable
Suppressed Lactation	676.41	Failure of lactation, delivered, with or without mention of antepartum condition

Condition	ICD-9 Codes	Text
Suppressed Lactation	676.42	Failure of lactation, delivered, with mention of postpartum complication
Suppressed Lactation	676.43	Failure of lactation, antepartum condition or complication
Suppressed Lactation	676.44	Failure of lactation, postpartum condition or complication
Suppressed Lactation	676.5	Suppressed lactation
Suppressed Lactation	676.50	Suppressed lactation, unspecified as to episode of care or not applicable
Suppressed Lactation	676.51	Suppressed lactation, delivered, with or without mention of antepartum condition
Suppressed Lactation	676.52	Suppressed lactation, delivered, with mention of postpartum complication
Suppressed Lactation	676.53	Suppressed lactation, antepartum condition or complication
Suppressed Lactation	676.54	Suppressed lactation, postpartum condition or complication
Suppressed Lactation	676.8	Other disorders of lactation
Suppressed Lactation	676.80	Other disorders of lactation, unspecified as to episode of care or not applicable
Suppressed Lactation	676.81	Other disorders of lactation, delivered, with or without mention of antepartum condition
Suppressed Lactation	676.82	Other disorders of lactation, delivered, with mention of postpartum complication
Suppressed Lactation	676.83	Other disorders of lactation, antepartum condition or complication
Suppressed Lactation	676.84	Other disorders of lactation, postpartum condition or complication
Suppressed Lactation	676.9	Unspecified disorder of lactation
Suppressed Lactation	676.90	Unspecified disorder of lactation, unspecified as to episode of care or not applicable
Suppressed Lactation	676.91	Unspecified disorder of lactation, delivered, with or without mention of antepartum condition
Suppressed Lactation	676.92	Unspecified disorder of lactation, delivered, with mention of postpartum complication
Suppressed Lactation	676.93	Unspecified disorder of lactation, antepartum condition or complication
Suppressed Lactation	676.94	Unspecified disorder of lactation, postpartum condition or complication