Janssen Research & Development on behalf of the Domperidone Collaboration Study Group*

European Union Non-interventional Post-Authorisation Safety Study (EU-PASS)

A Drug Utilisation Study of Domperidone in Europe Using Databases

Protocol RRA-17006

Domperidone

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EU PAS Register Number: EUPAS16062

PRINCIPAL INVESTIGATOR: Susan A. Oliveria, ScD, MPH, FISPE, QuintilesIMS, New York, NY; USA

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: Daniel Fife, MD, Janssen R&D, Titusville, NJ; USA

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Compliance: This study was conducted in compliance with the protocol and applicable regulatory requirements.

PASS INFORMATION

Title:	A Drug Utilisation Study of Domperidone in Europe Using Databases
Version identifier of the final study report:	1.0
Date of last version of the protocol:	20 July 2016
EU PAS Register No:	EUPAS16062
Active substance (INN common name):	domperidone
Pharmacotherapeutic group (ATC Code):	A03FA03
Medicinal product(s):	domperidone
Product reference:	ATC code: A03FA03
Procedure number:	EMEA/H/N/PSP/J/0031
Name of 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: • Prescribing for on-label indication; • Duration of use ≤7 days; • Dose no higher than recommended (30 mg for adults, 0.25 mg/kg TID for children); • No concomitant use of medications that prolong the QT-interval or are potent CYP3A4 inhibitors; and • No prescribing to patients with contraindicated conditions, e.g., moderate or severe liver disease, underlying cardiac diseases.
Country(-ies) of study	Belgium, France, Germany, Spain, and the United Kingdom
Author	The DUS protocol subcommittee of the Domperidone Collaboration Study Group

MARKETING AUTHORISATION HOLDER(S)

Name of Marketing Authorisation Holder:	Janssen Research & Development on behalf of the Domperidone Collaboration Study Group
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Contact Details:	Maarten Theuwissen, Global Regulatory Affairs, mtheuwi1@its.jnj.com A complete list of Marketing Authorisation Holders can be found in Section 4

Principal Investigator:

Name:	Susan A. Oliveria, ScD, MPH, FISPE
Signature:	
Date:	12/15/2017

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1. ABSTRACT

Name of Sponsor/Company	Janssen Research & Development on behalf of the Domperidone Collaboration Study Group*
Name of Finished Product	domperidone
Name of Active Ingredient(s)	domperidone

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Protocol No.: RRA-17006

Title of Study: A Drug Utilisation Study of Domperidone in Europe Using Databases (V2, 20 July 2016)

Sponsor's Responsible Medical Officer: Daniel Fife, MD, Janssen R&D, Titusville, NJ; USA

Keywords: domperidone, risk minimisation measures, drug utilisation study

EU PAS Register Number: EUPAS16062

Marketing Authorisation Holder(s): Janssen Research & Development on behalf of the Domperidone Collaboration Study Group (for a complete list of MAHs, see Section 4)

Names and Affiliations of Principal Investigator(s): Susan A. Oliveria, ScD, MPH, FISPE, QuintilesIMS, New York, NY; USA

Study Center(s): Belgium, France, Germany, Spain, and the United Kingdom

Publication (Reference): None

Study Period: 1 January 2011 to 30 September 2015

Background and Rationale: In March 2013, the European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) initiated a review of domperidone-containing medicines over concerns about cardiac adverse effects of domperidone. Subsequently, the PRAC recommended that the product label of domperidone-containing medicines be updated to strengthen the information regarding cardiac risks. In addition, the PRAC raised concerns that there may be off-label use for the stimulation of lactation and for the treatment of gastro-oesophageal reflux disease, gastroparesis, symptoms of postural hypotension in Parkinson's disease patients, and inflammatory bowel syndrome. The PRAC also recommended lowering the maximum daily dose to 10 mg "ter in die" (TID, which translates to "three times a day") in adults and 0.25 mg/kg TID in children <35 kg and limiting duration of use to ≤7 days. Within the context of risk minimisation measures, the PRAC requested that the domperidone market authorisation holders 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.

Research Question and Objectives: The primary objectives were to describe the prescribing patterns before and after the changes to the domperidone label and distribution of the Direct Healthcare Professional Communication (DHPC) and estimate and compare the overall proportion of domperidone prescriptions before and after implementation of the risk minimisation measures regarding the composite endpoint, which consisted of the following components (label requirements): prescribing for on-label indication, duration of use ≤7 days, dose no higher than recommended, no concomitant use of medications that prolong the QT-interval or are potent CYP3A4 inhibitors, and no prescribing to patients with selected contraindicated conditions. The secondary objectives were to estimate the overall proportion of domperidone prescriptions before and after implementation of risk minimisation measures for domperidone for each of the *individual* components of the composite endpoint, the time trend of apparent indication, days' supplied (≤7 days vs. >7 days), and age and sex of the patients receiving domperidone prescriptions.

Study Design: This was a post-authorisation, retrospective, observational cohort study using a pre- and post-design to examine the changes in the prescribing patterns of domperidone. A cohort of patients receiving domperidone was identified from existing secondary data sources (QuintilesIMS, Clinical Practice Research Datalink [CPRD]) in Belgium, France, Germany, Spain, and the United Kingdom (UK).

Setting: The study period was from 1 January 2011 through 30 September 2015 and was divided into 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 6-month implementation period of risk minimisation measures (1 April 2014 through 30 September 2014), and a 1-year post-implementation period of risk minimisation measures (1 October 2014 through 30 September 2015).

Patient Population and Study Size: Patients were included if they had at least 1 prescription for domperidone (outpatient setting) during any pre-defined study period and were registered with the practice and had available medical history for at least 180 days. Study size varied according to country and data source. All patients available in the study population were considered for the analysis.

Variables and Data Sources: Demographic characteristics (age and sex) were collected and summarised. The 5 label requirements were examined as a composite endpoint ("all label requirements") and individually.

Statistical Methods: Data analysis in the study was descriptive. The rates for the composite endpoint were calculated as the number of domperidone prescriptions consistent with the revised label per 1,000 domperidone-treated patients and as a proportion of overall domperidone prescriptions. The composite endpoint was estimated 4 ways to address uncertainty about unknown indication and duration of use. In the optimistic scenario, unknown indication was assumed to be nausea and vomiting and duration of use was assumed to be ≤7 days. In intermediate scenario-A, unknown indication was assumed to be an off-label indication and duration of use was assumed to be ≤7 days. In intermediate scenario-B, unknown indication was assumed to be nausea and vomiting and duration of use was assumed to be the days' supply. In the pessimistic scenario, unknown indication was assumed to be an off-label indication and duration of use was assumed to be the days' supply. Rates were calculated for each individual component of the composite endpoint. Rates of the pre-implementation composite endpoint were compared with rates of the post-implementation composite endpoint using risk ratios (RRs). In addition, each *individual* component of the composite endpoint was compared for the same two periods using RRs. Finally, the apparent indications, days supplied (≤7 days vs. >7 days), and demographic characteristics of the study population (sex, age group) were tabulated. Adult and paediatric patients were described separately.

RESULTS:

Overall, results of the composite endpoint varied by scenario and country. For the optimistic scenario, a moderate improvement in compliance with all label requirements was observed for most countries, with the exception of France, which demonstrated a large improvement. Results for intermediate scenario-A were inconclusive. Risk ratios ranged from a small improvement in compliance (Belgium) to a large improvement in compliance (France), however, no conclusions could be drawn for Germany, Spain, or the UK due to the small proportions of prescriptions meeting all label requirements. The findings for intermediate scenario-B were mostly positive and ranged from a modest improvement in compliance (UK) to a large improvement in compliance (France, Germany), however, no conclusions could be drawn for Belgium or Spain due to the small proportions of prescriptions meeting all label requirements. The findings for the pessimistic scenario were inconclusive. No conclusions could be drawn for any country due to the small proportions of prescriptions meeting all label requirements.

Examination of the individual components of the composite endpoint revealed that in most countries compliance was high for the no contraindicated medications and no contraindicated conditions label requirements and was moderate to high for the maximum daily dose label requirement. Compliance with these 3 label requirements did not change appreciably from the pre- to the post-implementation period, except for France where there was dramatically improved compliance with the maximum daily dose label requirement in the post-implementation period. There was mixed compliance across the countries with the

on-label indication (in the analysis where unknown/other indication was assumed nausea and vomiting). Most countries had poor compliance with on-label indication (in the analysis where unknown/other indication was assumed off-label) and duration of use ≤7 days (as represented by days' supply ≤7 days).

Results for paediatric patients and patients aged 12-14 years weighing <35 kg were inconclusive for most countries either due to small sample size or the small proportions of prescriptions meeting all label requirements. However, France demonstrated large improvements in complying with all label requirements across all scenarios, primarily driven by improvements in compliance with the duration of use ≤7 days, maximum daily dose, and on-label indication (where unknown/other indication was assumed off-label).

DISCUSSION

Due to the heterogeneity of the results, it is difficult to determine what effect, if any, the risk minimisation measures had on off-label prescribing of domperidone. Results suggest that most domperidone prescriptions had an unknown or other diagnoses indication. This was likely because healthcare providers do not regularly enter indication for prescriptions or ensure that indication is entered correctly (Belgium, France, and Spain) and that Germany and UK data sources do not have an indication field explicitly associated with the prescription. Therefore, the 4 scenarios either overestimated (optimistic scenario, intermediate scenario-B) or underestimated (intermediate scenario-A, pessimistic scenario) compliance with the on-label indication label requirement as a result of the "all or nothing" approach to classifying prescriptions with an unknown or other diagnosis as either all on-label or all off-label. Additionally, most of the domperidone prescriptions had a days' supply >7 days, possibly as a result of how medications are packaged and dispensed and/or reimbursed in the 5 countries. Furthermore, since domperidone is used as needed, some healthcare providers may prescribe extra doses for future use. Also, in some countries, the cost to the patient of a 30 days' supply was identical to the cost of a 7 days' supply. Therefore, actual duration of use was unknown for a large percentage of domperidone prescriptions and the 4 scenarios either overestimated or underestimated compliance with the duration of use ≤7 days label requirement as a result of the "all or nothing" approach to classifying prescriptions as either all duration of use ≤7 days (i.e., on-label) or setting the duration of use equal to the days' supply as written on the prescription.

There are inconsistent data in the literature to support the effectiveness of safety warnings and DHPC letters on changing prescribing behavior. In this study, with the exception of France, it appears that the risk minimisation measures had minimal to no effect on improving the on-label prescribing of domperidone. However, these results should be interpreted in the context that true duration of use and true indication were not known for a large percentage of domperidone prescriptions. Although the intent of the study design was to address these uncertainties by assessing domperidone utilisation under 4 scenarios, limitations in the data and small sample size for the paediatric patients and patients aged 12-14 years weighing <35 kg, made it difficult to overcome the uncertainty of indication and duration.

CONCLUSIONS:

Overall, it was difficult to draw any conclusions regarding the effect of the risk minimisation measures on compliance with on-label prescribing of domperidone, with the possible exception of the results for France, which showed improvements across most scenarios for all patient populations. For the other countries, however, a significant number of domperidone prescriptions were missing data for indication and/or duration of use due to the limitations associated with the secondary data sources. Therefore, our ability to approximate the truth of how domperidone was prescribed via the 4 scenarios was limited. Sample size prohibited drawing any conclusions for the paediatric patients in Belgium, Germany, Spain, and the UK.

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

CPRD	Clinical Practice Research Datalink
DHPC	Direct Healthcare Professional Communication
EMA	European Medicines Agency
EMR	electronic medical record
EU	European Union
GERD	gastro-oesophageal reflux disease
GP	general practitioner
IBS	inflammatory bowel syndrome
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
kg	Kilogram
LPD	Longitudinal Practice Database
MA	market authorisation
MAHs	market authorisation holders
mg	Milligram
PRAC	Pharmacovigilance Risk Assessment Committee
PRN	“pro re nata,” which translates to “when necessary”
RR	risk ratio
SmPC	Summary of Product Characteristics
TID	"ter in die," which translates to “three times a day”

Definition of Term(s)

Study	The term “study” indicates the collection of data for research purposes only. The use of this term in no way implies that any interventional treatments or procedures, planned or otherwise, have been provided or performed.
Retrospective non-interventional study	A study that has all information collected from source data or a retrospective database. Normally, there is no new collection of information from the patient, although this may be required to address specific questions. Studies/Programmes/Related Research Activities with only one visit can be considered prospective or retrospective bearing in mind this definition and the source of information.
Post-Authorisation Safety Study (PASS)	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

3. INVESTIGATORS

Principal Investigator: Susan A. Oliveria, ScD, MPH, FISPE

4. OTHER RESPONSIBLE PARTIES

Sponsor's Responsible:

Medical Officer:	Daniel Fife, MD*
Statisticians:	Peter Hu, PhD*
Medical Writer:	Karyn Frey*
Contract Research Organization and level of involvement:	QuintilesIMS; data collection, analysis, and reporting

* Considered an author of this report

List of MAHs

Party (*: Party itself does not hold a MA)	MAH Affiliates
Accord Healthcare Ltd.	
ABC Farmaceutici S.p.A.	
Actavis Group PTC ehf.	Actavis Nordic A/S Actavis Group hf.
Aventis Pharma Ltd	Sanofi Aventis France Winthrop Pharmaceuticals UK Ltd
ARISTO Pharma GmbH Represented by: Luica Rossi	
Aurobindo Pharma Ltd	Pharmacin B.V. – Arrow Generiques SAS – Aurovitas Unipessoal Lda. Milpharm Ltd. Aurobindo Pharma B.V. Sofar S.p.A. Netherlands Sofar S.p.A. Italy Alternova A/S
Laboratorios Azevedos – Indústria Farmacêutica S.A.	
Betapharm Arzneimittel GmbH	
Biogaran	
Bristol Laboratories Ltd.	
DOC Generici S.r.l.	
Laboratorios del Dr. Esteve S.A.U.	
Focus Pharmaceuticals Ltd.	
Generis Farmaceutica S.A.	
Laboratoires Gerda SAS	
Giuliani S.p.A.	
Hexal AG	1 A Pharma GmbH Rowex Ltd. Sandoz N.V. Sandoz Farmaceutica LDA. Sandoz SAS Sandoz S.p.A. Sandoz B.V.
Italchimici S.p.A.	
Johnson & Johnson Consumer NV/SA	Janssen-Cilag Pharma GmbH

Party (*: Party itself does not hold a MA)	MAH Affiliates
	Johnson & Johnson, prodaja Medicinskih in farmacevtskih Izdelkov, D.O.O. Janssen-Cilag International NV Janssen-Cilag s.r.o. Janssen-Cilag A/S Janssen-Cilag SA Janssen-Cilag Johnson & Johnson Hellas Consumer AE Janssen-Cilag Kft. McNeil Healthcare (Ire) Ltd Janssen-Cilag S.p.A. UAB Johnson & Johnson Johnson & Johnson Consumer BV Johnson & Johnson Lda
Kela Pharma NV	
MEDA Pharma S.L	
Laboratorio Medinfar – Produtos Farmeceuticos SA	GP - Genericos Portugueses Lda
Manx Healthcare Ltd	
Mylan EMEA SAS	Mylan BVBA/SPRL Mylan SAS Mylan S.p.A. Mylan BV Mylan Lda
Pensa Pharma SA	Pensa Pharma S.p.A. Tolife Produtos Farmaceuticos SA
Pierre Fabre Médicament SAS	Pierre Fabre ϕ APMAKA A.E. Pierre Fabre Pharma SRL
S.F. Group Srl	
Stada Arzneimittel AG	Aliud Pharma GmbH Centrafarm BV Ciclum Farma Unipessoal Lda Clommel Healthcare Ltd Crinos S.p.A. EG S.p.A. EG Labo Laboratoires EuroGenerics Eurogenerics NV/SA Healthypharm BV STADA Arzneimittel AG STADApharm GmbH STADA d.o.o.
Strides Shasun (UK) Ltd	
Takeda GmbH	
Terapia SA	
Teva Pharmaceuticals Europe BV *	AbZ-Pharma GmbH Mediq Farma BV Pharmachemie BV Ratiopharm Lda Teva Pharma Belgium NV Teva GMBh Teva Italia Srl Pharmachemie BV Teva Santé SAS
Wockhardt UK Ltd	
Zydus France SAS	

5. MILESTONES

The dates for key milestones in this study are outlined below.

Milestone:	Planned Date:	Actual Date:	Comments:
ISAC ethical approval		02 February 2017	
Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS) ethical approval		15 May 2017	
Start of data collection	Two months after protocol approval	27 February 2017	Data collection began after the statistical analysis plan was approved
End of data collection	When data through SEP2015 become available for analysis (estimated as 4Q2016)	22 May 2017	
Registration in the EU PAS register	Before the start of the study	7 December 2016	
Final report of study results*	Twelve months after the end of data collection		

*Timing of final report included 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

6. BACKGROUND AND RATIONALE

Domperidone is a gastrointestinal motility agent effective in the treatment of acute nausea and vomiting and was first approved in Belgium in March 1978.

In 2011, the European Union (EU) Pharmacovigilance Working Party recommended that the product information for domperidone-containing medicines be updated to reflect the risk of adverse cardiac effects of domperidone, including QT prolongation, arrhythmias, and sudden cardiac death. In response to this recommendation, the Summary of Product Characteristics (SmPC) was updated in 2012 to include QT prolongation as an adverse drug reaction.

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, under Article 31 of Directive 2001/83/EC, over concerns about cardiac adverse effects of domperidone. Subsequently, the PRAC recommended that the product label (SmPC and Patient Information Leaflet) of domperidone-containing medicines be updated to strengthen the information regarding cardiac risks. In addition, the PRAC raised concerns that there may be off-label use of domperidone for the stimulation of lactation in breastfeeding women and for the treatment of gastro-oesophageal

reflux disease (GERD), diabetic and non-diabetic gastroparesis, symptoms of postural hypotension in Parkinson's disease patients, and inflammatory bowel syndrome (IBS).

The recommendations after conclusion of the Article 31 referral were as follows:

- Restriction of the indication to nausea and vomiting;
- Limitation of duration of use to 7 days;
- Reduction of the maximum daily dose to 10 milligram (mg) "ter in die" (TID, which translates to "three times a day") for adults and adolescents (12 years of age and older and weighing 35 kilograms (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 Co-ordination Group for Mutual Recognition and Decentralised Procedures 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 market authorisation holders (MAHs) distributed a Direct Healthcare Professional Communication (DHPC) and updated the SmPC. The PRAC requested that the 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. This study is one of two studies designed to answer the PRAC's request. In addition to a separate physician survey conducted to assess the prescribers' understanding, knowledge, and awareness of the new safety information on domperidone, the current study was conducted to describe domperidone utilisation patterns. This report describes the results from a drug utilisation study using healthcare databases in 5 EU countries.

7. RESEARCH QUESTION AND OBJECTIVES

Research Question

The objective of the study was 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 EU countries.

Objectives

The primary objectives for this study were:

- To describe the prescribing patterns before and after the changes to the domperidone label and distribution of the DHPC and estimate and compare the overall proportion of domperidone prescriptions before and after implementation of the risk minimisation measures regarding the following measure:
  - Composite endpoint consisting of the following components:

- Prescribing for on-label indication;
- Duration of use ≤7 days;
- Dose no higher than recommended;
- No concomitant use of medications that prolong the QT-interval or are potent CYP3A4 inhibitors; and
- No prescribing to patients with contraindicated conditions, e.g., moderate or severe liver disease, underlying cardiac diseases.

The secondary objectives for this study were 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;
- Time trend of apparent indication and days' supplied (≤7 days vs. >7 days); and
- Age and sex of the patients receiving domperidone prescriptions.

8. AMENDMENTS AND UPDATES

No amendments were implemented.

9. RESEARCH METHODS

9.1. Study Design

9.1.1. Overview of Study Design

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

A cohort of patients prescribed domperidone were identified from the following existing secondary data sources: QuintilesIMS databases for Belgium, France, Germany, and Spain and the Clinical Practice Research Database (CPRD) for the United Kingdom (UK).

9.1.2. Changes in Conduct

There were no changes to the conduct of the study.

9.2. Setting

The study period was from 01 January 2011 through 30 September 2015 and was divided into a background period, a pre- and post- implementation period[a] of risk minimisation measures, and an implementation period as follows:

- A background period (01 January 2011 through 31 March 2013);

[a] The background period, pre-implementation period, implementation period, and the post-implementation period are termed "pre-defined study periods" when referring to all study periods.

- A 1-year pre-implementation period of risk minimisation measures (01 April 2013 through 31 March 2014);
- A 1-year post-implementation period of risk minimisation measures (01 October 2014 through 30 September 2015); and
- The period during which the label change took place and the DHPC was sent was used as the period during which the risk minimisation measures were implemented (01 April 2014 through 30 September 2014).
  - Please note that while the DHPC letter was sent on different dates in different countries, the implementation period (termed the risk minimisation period in Figure 1) covered the entire time period that risk minimisation measures were implemented and was the same for all countries.

Figure 1: Study Period

Because the amendments to the product information were suggested by the Pharmacovigilance Working Party in October 2011, the study tracked prescribing pattern changes from 01 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. Patient Population

The study population was defined as all patients receiving domperidone in the outpatient setting during the pre-defined study periods in Belgium, France, Germany, Spain, and the UK. Patients were included in the study cohort if they had at least 1 prescription for domperidone in the selected databases during the overall study period and had membership or had been registered (or the equivalent of) with the practice and had available medical history for at least 180 days before the domperidone prescription.

The date of the first prescription of domperidone in the overall study period was defined as the index date. All domperidone prescriptions were included in analyses if the date of the prescription was between the index date and the end of the study period. Prescriptions for patients were assessed from the index date to the earliest of the following dates:

- End of the study period;
- Patient transfer out of a practice represented in the database; and
- 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).

9.3.1. Inclusion and Exclusion Criteria

The following were the study inclusion criteria:

- ≥1 prescription for domperidone in the outpatient setting; and
- Had membership or had been registered (or the equivalent of) with the practice and had available medical history for ≥180 days before the domperidone prescription.

No exclusion criteria were applied.

Domperidone was identified by Anatomical Therapeutic Classification (ATC) code or British National Formulary (BNF) chapter code. For a list of codes used to identify domperidone, see Section 19 (Annex 2.5)

9.4. Variables

9.4.1. Baseline Variables

The topics in this section summarise the baseline variables collected, definitions, and methodology used for identifying the variables in the electronic medical record (EMR) data. Unless otherwise specified, each country followed the methods outlined in the following topics. Where other methods were used due to data availability, the method and the country/data source is specified.

Age

In all databases, age was available as year of birth (YOB). Age was calculated as date of the first domperidone prescription in a study period minus the YOB, using 1 January as the day and month for every country. Age was calculated separately for each of the four time periods.

If there were multiple prescriptions for a patient in a pre-defined study period (e.g., 1 prescription in April 2011, 1 prescription in June 2012, and 1 prescription in February 2013, all of which fell in the background period) then age was calculated at the middle of each time period.

Age was reported as a continuous and categorical variable.

Age categories were: 0-3, 4-11, 12-17, 18-30, 31-40, 41-50, 51-60, 61-70, 71-80, >80, and Unknown.

If a patient had an age ≥110 years, then age was classified as "Unknown."

Sex

The definition and categories for sex were: male, female, and unknown.

Geographic region

The definition of geographic region was county and the categories were: Belgium, France, Germany, Spain, and the UK.

Geographic region was determined by the data source (e.g., Disease Analyzer data was from Germany, CPRD data was from the UK). No actual data was extracted for geographic region.

9.4.2. Primary Domperidone Therapy

9.4.2.1. Indication

If a data source had a field for indication for a prescription, and if it was completed, then the recorded indication was used. For example, in Belgium, France, and Spain, most prescriptions were recorded with a diagnosis code for indication. However, in Germany, while healthcare providers are encouraged to link diagnoses with prescriptions, only approximately 50% of prescriptions are linked with a diagnosis code and, in the UK, prescriptions were not explicitly recorded with a diagnosis code for indication.

For prescriptions without a recorded diagnosis code for indication, indication was estimated from the presence of ≥1 diagnosis code (International Classification of Diseases, Ninth Revision, Clinical Modification[a] (ICD-9-CM), International Classification of Diseases, Tenth Revision, Clinical Modification[b] (ICD-10-CM), or Read[c]) recorded in the specified time period preceding each domperidone prescription.

Diagnosis collected for indication was:

- Nausea and vomiting;
- GERD;
- Abdominal bloating, gastric dysmotility, delayed gastric emptying (termed "gastroparesis" in this report);
- IBS;
- Suppressed lactation, failed lactation, lactation not established, decreased lactation, lactation problem (termed "an aid to lactation" in this report); and
- Orthostatic hypotension and a diagnosis of Parkinson's disease (termed "symptoms of postural hypotension in Parkinson's disease patients" in this report).[d]
- Unknown or other: For those prescriptions not classified as above or without an indication recorded, the indication was classified as "Unknown or other"

[a] ICD-9 diagnosis codes were only used in Spain.

[b] ICD-10 diagnosis codes were only used in Belgium, France, and Germany. In Germany, the Disease Analyzer only contains 4 digits for the ICD-10 code.

[c] Read codes were only used in the UK.

[d] Because the Germany Disease Analyzer prescriptions can only have 1 linked diagnosis, a diagnosis of orthostatic hypotension can never occur in conjunction with Parkinson's disease. Therefore, in Germany, if either orthostatic hypotension or Parkinson's disease was the linked diagnosis with the domperidone prescription, then the other diagnosis was looked for in the two months prior to the domperidone prescription.

If there were multiple diagnoses of interest recorded for a prescription, in the absence of a nausea and vomiting diagnosis, then all of the diagnoses of interest were recorded. For example, if a prescription had a diagnosis of GERD and IBS associated with it (but not a diagnosis of nausea and vomiting) then both the GERD and the IBS diagnosis were recorded. However, if there was a diagnosis of nausea and vomiting, regardless of the presence of any additional diagnoses, the indication was classified as "nausea and vomiting" only.

The timeframe for the diagnoses was defined as follows:

- Nausea and vomiting —on the day of the prescription or in the preceding 7 days;
- 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—in the 2 months up to and including the date of domperidone prescription—and in the absence of a diagnosis of nausea and vomiting; and
- Unknown or other—if the prescription had not been classified as previously described.

For a list of the diagnostic terms and codes that were used to identify diagnoses, see Section 18 (Annex 2.4).

9.4.2.2. Duration of Treatment

The duration of each prescription was estimated from the days' supply, if available, or calculated directly as the total prescription quantity prescribed divided by daily number of pills recommended in the dosing instructions.

In Belgium, France, and Spain, there is a specific field in the EMR for the general practitioner (GP) to provide a duration for the prescription, which was either specified in number of days, weeks, or months or in number of packs prescribed. If the duration of the prescription was specified in number of packs prescribed, then duration was calculated by taking the number of units prescribed and dividing by the daily dose (see below). Duration was always reported in number of days, regardless of how it was originally specified on the prescription. For example, if a patient was prescribed a medication for 2 months, this duration was converted to 60 days for the analyses. If the GP filled in the duration variable with a "0," then duration was recorded as missing.

In the UK, the duration variable, "number of days" (numdays) was used. If this variable was missing, duration was calculated by taking the quantity prescribed and dividing by the daily dose indicated (qty/ndd).

$$\text{duration} = \frac{\text{number of units prescribed}}{\text{daily dose}} \Leftrightarrow \frac{\text{quantity prescribed (qty)}}{\text{daily dose indicated (ndd)}}$$

In the Disease Analyzer Germany, there is no duration variable. Instead, the recorded dosage recommendation was used to calculate duration, as shown below. Approximately one-third of the domperidone prescriptions in the Disease Analyzer had a recorded dosage recommendation, which was recorded with the first prescription. For these prescriptions, the recommended dose

was carried forward until there was evidence that it had changed and then the new recommended dose was carried forward. Patients without a recorded dosage recommendation were not included in the study.

Duration was calculated by multiplying the package size by the number of packages and dividing by the number of tablets recommended per day:

$$\text{duration} = \frac{\text{package size (i.e., number of tablets)} \times \text{number of packages}}{\text{recommended number of tablets per day}}$$

If a patient had overlapping domperidone prescriptions and the dose of the second prescription was different from the first prescription (i.e., lower or higher), then it was assumed that the patient had stopped taking the first prescription and was now taking the second prescription. The days' supply of the first prescription was then truncated at the date of the second prescription.

If the dose of the second prescription was the same as the first prescription, then it was assumed that the prescriptions were taken consecutively. In this scenario, the days' supply of either prescription was not truncated.

9.4.2.3. Dose per day

The dose per day for adults and children who took the oral tablet or oral suspension was calculated as described in the following sections.

Belgium, France, and Spain

The formula was:

$$\text{number of intakes by day} \times \text{dose by intake}^{a}$$

For example, if an adult was prescribed 3 intakes per day and each intake was 10 mg, then the dose per day was calculated as: $3\ \text{intakes/day} \times 10\ \text{mg/intake} = 30\ \text{mg/day}$

Germany

The formula was:

$$\text{recommended number of tablets (or mL) per day} \times \text{strength (Germany)}$$

For example, if an adult was prescribed 3 tablets per day at a strength of 10 mg, then dose per day was calculated as: $3\ \text{tablets/day} \times 10\ \text{mg/each} = 30\ \text{mg/day}$

UK

The formula was:

[a] If the GP filled in a "0" for any of these variables, then the dose per day was recorded as missing.

$$\frac{\text{quantity} \times \text{strength}}{\text{days' supply}} \Leftrightarrow \frac{\text{total mL}}{\text{days' supply}} \text{ (UK)}$$

For example, if an adult was prescribed a total of 210 mL oral suspension for 7 days, then the dose per day was calculated as:

$$\frac{210 \text{ mL}}{7 \text{ days}} = 30 \text{ mL/day}$$

All Countries

If the prescription contained a range of tablets, dosage, and/or duration, the average value of each was used for the calculation of dose per day. For example, "take 1-2 tablets, 2-3 times per day" was converted to "take 1.5 tablets, 2.5 times per day."

If there were multiple domperidone prescriptions on the same date for the same person, all prescriptions were kept and evaluated separately.

For adults and adolescents and children ≥12 years of age (who were or were assumed to be greater than or equal to 35 kg[a,b]), their dose per day was compared to the maximum recommended dose per day of 10 mg TID (i.e., 30 mg/day) for the oral tablet or 10 mL TID (i.e., 30 mL/day) for the oral suspension.

For adolescents and children 12-14 years of age (who were less than 35 kg) and children <12 years of age (who were less than 35 kg, see explanation in following paragraph), their dose per day was compared to the maximum recommended dose per day for their weight, which was calculated as:

$$\left[\text{weight (kg)} \times 0.25 \frac{\text{mg}}{\text{kg}} \times 3\right] \Leftrightarrow \left[\text{weight (kg)} \times 0.25 \frac{\text{mL}}{\text{kg}} \times 3\right]$$

For example, for a child who weighs 10 kg, the recommended maximum dose per day would be:

$$10 \text{ kg} \times 0.25 \frac{\text{mg}}{\text{kg}} \times 3 = 7.5 \text{ mg/day}$$

Adolescents and children 12-14 years of age weighing less than 35 kg had their dose per day compared to the maximum recommended dose per day for their weight while adults and children

[a] The availability of weight varied by country; in Belgium, France, and Spain this field was completed 20-50% of the time (depending on country) and weight was less commonly recorded for adults and more commonly recorded for children. In Germany, weight was poorly recorded and completed approximately 10-20% of the time. In the UK, a recent study found that weight for adults was recorded in the past 3 months approximately 50% of the time while weight for paediatric patients was completed at almost every visit.

[b] Adults and adolescents and children ≥12 years of age who did not have a weight recorded within 1 year of the domperidone prescription were assumed to be greater than or equal to 35 kg.

≥12 years of age without a recorded weight were assumed to be ≥35 kg and, therefore, had their dose per day compared to the maximum recommended dose of 30 mg per day.

For all calculations that required weight, the weight must have been recorded within 1 year prior to the domperidone prescription. Children <12 years of age who did not have a weight recorded within 1 year of the domperidone prescription were excluded from the analyses that required dose per day to be known. Adults and adolescents and children ≥12 years of age who did not have a weight recorded within 1 year of the domperidone prescription were assumed to be greater than or equal to 35 kg.

All data was included in the analyses, even if it appeared that there were outliers in the data (e.g., a patient who was prescribed 42 tablets per day).

9.4.2.4. Concomitant use With Select Medications

Duration of domperidone use was needed to assess concomitant use with selected medications, however, because domperidone is used as needed, the duration of use may not be the same as the number of days for which domperidone was supplied. As a result, duration of use was assessed under the following 2 scenarios, which would be likely to bracket the actual (but unknown) situation:

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

To assess the first scenario, concomitant medication use was defined as ≥1 prescription for a medication that prolongs the QT interval or is a potent CYP3A4 inhibitor that occurred *on or prior to the date of the domperidone prescription* —and— where the duration of use overlapped with the domperidone prescription for at least one day (in this scenario, only one day of overlap was possible).

To assess the second scenario, concomitant medication use was defined as ≥1 prescription for a medication that prolongs the QT interval or is a potent CYP3A4 inhibitor that occurred *on or prior to the date of the domperidone prescription* —and— where the duration of use overlapped with the days' supply of the domperidone prescription for at least one day *or during the days' supply of the domperidone prescription*.

There was a 30-day lookback period from the date of the domperidone prescription through the end of the days' supply for possible prescriptions concomitant with the domperidone prescription.

Concomitancy was defined as exposure (Yes/No) to a medication that prolongs the QT interval or is a potent CYP3A4 inhibitor that was prescribed before or on the date of the domperidone prescription or during the days' supply of the domperidone prescription with ≥1 overlapping days' supply. Medication exposure was determined by Anatomical Therapeutic Classification or British National Formulary codes, as appropriate.

For a list of medications that are known to prolong the QT interval, see Section 20 (Annex 2.6) and Section 21 (Annex 2.7).

For a list of medications that are potent or strong CYP3A4 inhibitors, see Section 22 (Annex 2.8) and Section 23 (Annex 2.9).

Note: There was likely incomplete capture of concomitant medications because secondary databases reflect the records of medical practices and often cannot link patients across multiple practices. Therefore, prescriptions written by other prescribers were likely not captured. For example, in the UK some concomitant medications (e.g. HIV drugs ritonavir/lopinavir) are prescribed at a specialist centre and, therefore, unlikely to be recorded in the CRPD.

9.4.2.5. Contraindicated Conditions

Contraindicated conditions were a diagnosis of one or more of the following:

- Hepatic cirrhosis;
- Hepatic failure;
- Hepatic coma;
- QTc prolongation;
- Ventricular arrhythmia;
- Congestive heart failure; and/or
- Hypokalemia.

For all contraindicated conditions, diagnoses were determined by ICD-10-CM diagnosis codes (Belgium, France, Germany), ICD-9-CM diagnosis codes (Spain), or Read codes (CRPD). (For a list of the codes, see Section 18 (Annex 2.4). However, the time period during which the codes were assessed differed by condition(s).

Hepatic cirrhosis, hepatic failure, or hepatic coma were identified between 1 January 2011 and 1 day before the prescription was written. We assumed that no patients had moderate/severe hepatic failure prior to 1 January 2011. Moderate/severe hepatic failure was assessed starting 1 January 2011.

QTc prolongation, ventricular arrhythmia, or congestive heart failure were identified in the 6 months prior to the domperidone prescription.

Hypokalemia was identified in the 30 days prior to the domperidone prescription.

9.4.2.6. Composite Endpoint/all Label Requirements

Each prescription was classified according to whether it appeared to meet all components of the composite endpoint, as follows:

- Prescribing for on-label indication;
- Duration of use ≤7 days[a];
- Dose no higher than recommended;
- No concomitant use of medications that prolong the QT-interval or are potent CYP3A4 inhibitors; and
- No prescribing to patients with contraindicated conditions, e.g., moderate or severe liver disease, underlying cardiac diseases.

Each prescription was evaluated regarding whether:

- Yes, the prescription met the composite endpoint; or
- No, the prescription did not meet the composite endpoint.

9.4.3. Outcomes

The primary outcomes of interest were:

- The proportion of domperidone prescriptions and rate per 1,000 domperidone-treated patients of meeting the composite endpoint in the pre- and post-implementation periods, estimated 4 ways to address uncertainty about unknown indication and duration of use; and
- The relative "risk" of a domperidone prescription meeting the composite endpoint (all label requirements[b]), comparing the post-implementation period to the pre-implementation period, estimated 4 ways to address uncertainty about unknown indication and duration of use.

The secondary outcomes of interest were:

- The proportion of domperidone prescriptions and rate per 1,000 domperidone-treated patients of meeting the individual components of the composite endpoint in the pre- and post-implementation periods;
- The relative "risk" of a domperidone prescription meeting the individual components of the composite endpoint, comparing the post-implementation period to the pre-implementation period;
- The distribution of indications of the patients receiving domperidone prescriptions in the pre- and post-implementation periods;
- The distribution of days' supplied (≤7 days vs. >7 days) of the patients receiving domperidone prescriptions in the pre- and post-implementation periods;
- The age distribution of the patients receiving domperidone prescriptions in the pre- and post-implementation periods; and

[a] All prescriptions for domperidone were treated as separate events and individually evaluated for compliance to the label requirements.

[b] For more information about the individual components of the composite endpoint, see Composite endpoint and Analysis of Secondary Objectives.

- The sex distribution of the patients receiving domperidone prescriptions in the pre- and post-implementation periods.

9.4.4. Evaluation of Safety

Adverse Events

This was a retrospective, observational, non-interventional study conducted using data from longitudinal EMR databases. As such, adverse events were not expected; however, a process was in place for adverse event reporting in the unlikely event that any were identified during data analyses.

9.5. Data Sources and Measurement

Patient information on domperidone exposure and study endpoints was obtained from the following longitudinal EMR databases:

- QuintilesIMS longitudinal patient EMR databases provide systematic ongoing information from physician office-based visits on patients' consultations, diagnoses, and treatment in Belgium, France, Germany, and Spain. They are:
  - QuintilesIMS EMR database Belgium
  - QuintilesIMS EMR database France
  - Quintiles IMS Disease Analyzer Germany
  - QuintilesIMS ER database Belgium
- CPRD: a longitudinal anonymised EMR 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.

Please note that:

- In Belgium, France, and the UK, data came from general practitioner (GP) providers only and included both adult and paediatric patients
- In Germany, data came from GP and Paediatric providers
- In Spain, data came from GP and Paediatric providers
- The countries were selected to include some 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 EMR databases in those countries.
- For additional details on the databases, see Section 17 (Annex 2.3).

9.6. Bias

- The databases often did not record the intended duration of use of each prescription. Instead, days' supply was used as a proxy for intended duration of use. This could have resulted in misclassification of drug exposure.

- Because domperidone is used as needed, missing information about the true duration of treatment was likely to be an important source of uncertainty in estimating compliance with the recommendation to limit use to ≤7 days and may have also been an important source of uncertainty about the frequency with which domperidone was used concurrently with a contraindicated medication. Additionally, depending on whether a patient decided to take or not take domperidone on a particular day, patients may have been classified as exposed when they were not actually taking the drug or unexposed when they were actually taking the drug.
- Since a substantial proportion of prescriptions did not either have a diagnosis or have a diagnosis that was plausible as an indication, there was appreciable uncertainty about the indications for which the medication was prescribed. Any attempt to obtain this missing information from chart review or questionnaires would have been subject to volunteer bias and there was no guarantee that the missing information on indication would have been recorded in a high proportion of the charts that were made available.

9.7. Study Size

The study size varied according to country and data source. All patients available in the study population were considered for the analysis. Preliminary estimates indicated that the suggested databases captured at least several thousands of domperidone prescriptions in each of the countries being studied.

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

Table 1 shows the approximate number of prescriptions needed for a study with the same number of prescriptions in the pre-implementation and the post-implementation periods to have 90% power to detect $p<0.05$ (2-sided test) risk ratios from 1.10 to 1.40 according to the risk during the pre-implementation period. Note that the "risks" are the probabilities of a prescription meeting all label requirements (composite endpoint); therefore, a risk ratio of 1.10 represents a 10% improvement in label compliance when comparing the post-implementation period to the pre-implementation period.

Table 1: Approximate Number of Subjects Required per Group (Before Implementation, After Implementation) Under Various Scenarios

"Risk" of complying with label before the implementation period	"Risk" Ratio = 1.10	"Risk" Ratio = 1.20	"Risk" Ratio = 1.30	"Risk" Ratio = 1.40
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 was as low as 10% in the pre-implementation period, then the study would have ≥90% power to detect a risk ratio of 1.10 (a 10% improvement) and smaller improvements would have been of limited public health interest. If compliance with the new label was higher than 10% in the pre-implementation period, then the study would have ≥90% power to detect smaller improvements in compliance with the new label requirements. All domperidone prescriptions that were captured during the study period, met the inclusion criteria, and were not missing any data required for the analysis of interest were included.

9.8. Data Transformation

The study used existing databases with anonymised information on the individual patients. Datasets and analytic programmes were stored according to QuintilesIMS procedures with access restricted to study personnel. The processes for database management differed by the data source. Data extraction and analysis were performed according to the standard practices of the data suppliers.

9.9. Statistical Methods

Statistical analyses were performed by or under the authority of the sponsor.

9.9.1. Main Summary Measures

Data analysis in the study was descriptive. Categorical variables were presented using percent and frequency tables. The rates, proportions, and risk ratios and corresponding 95% confidence intervals (CI) of all study endpoints (i.e., risk minimisation indicators) were calculated for the 2011-2015 period, using quarterly time blocks for the pre- and post- risk minimisation implementation periods. If a prescription extended into more than one quarterly time block, then it was counted only once in the quarterly time block that it was prescribed. The rates were calculated per 1,000 domperidone-treated patients and as a proportion of domperidone prescriptions. Mode of administration (i.e., formulation) was not considered.

Results are reported stratified by (1) adults and adolescents and children aged ≥12 years, (2) children aged <12 years, and (3) adolescents and children aged 12-14 years who are less than 35 kg.

For paediatric patients (i.e., children aged <12 years), the rates and proportions for all study endpoints (e.g., proportion of domperidone prescriptions meeting the “Dose no higher than recommended” endpoint) were calculated per 1,000 domperidone-treated paediatric patients and as a fraction of paediatric domperidone prescriptions.

For children 12-14 years of age who were less than 35 kg, the rates and proportions for all study endpoints were calculated per 1,000 domperidone-treated patients aged 12-14 years who were less than 35 kg and as a proportion of domperidone prescriptions prescribed to patients aged 12-14 years who were less than 35 kg.

Because paediatricians are less likely to record weight for older children, we also reported the number of patients aged 12-14 years, the number and percentage of patients aged 12-14 years with a recorded weight within 1 year prior to the domperidone prescription, and the number and percentage of patients aged 12-14 years with a recorded weight less than 35 kg within 1 year prior to the domperidone prescription for each of the pre-defined study periods[a].

In the CPRD, according to UK privacy rules for small number reporting, if results were small numbers (i.e., N<6), the small number was not reported. Small numbers are represented by *** in results tables.

All data analysis was done in SAS version 9.4 (SAS Institute, North Carolina, USA). Each country reported the results of the data analysis separately. No data were pooled.

9.9.2. Main Statistical Methods

9.9.2.1. Analysis of Primary Objectives

The primary test statistic estimated was the change in the proportion of all prescriptions that complied with the label (i.e., met all components of the composite endpoint; also referred to as "all label requirements") during the 12 months before the label change (i.e., the pre-implementation period) versus the 12 months after the label change (i.e., the post-implementation period) as a measure of the effectiveness of the label change. This test statistic was evaluated as a risk ratio, i.e., as the ratio of the proportion of prescriptions that met all components of the composite endpoint between 1 April 2013 and 31 March 2014 (i.e., the pre-implementation period) and the proportion of prescriptions that met all components of the composite endpoint between 1 October 2014 and 30 September 2015 (i.e., the post-implementation period). The risk ratio was calculated as follows:

$$\frac{\frac{\mathrm{RxMet}_{\mathrm{post}}}{\mathrm{RxAll}_{\mathrm{post}}}}{\frac{\mathrm{RxMet}_{\mathrm{pre}}}{\mathrm{RxAll}_{\mathrm{pre}}}}$$

Please note that the protocol was equivocal regarding how to calculate the risk ratio and that this method, described above, represents the approach documented in the statistical analysis plan for how to interpret the protocol and is included in the report for clarity.

The point estimate and 95% CI for the risk ratio are reported. Note that the term "risk" ratio (RR) is being used in the sense of a ratio of probabilities (the probability of a prescription being consistent with the new label).

[a] The denominator for both percentages reported was the total number of adolescents and children aged 12-14 years.

Note: If there was a small number (≤5) or a small proportion (≤5%) of prescriptions that met all label requirements or each individual label requirement in the pre- and/or post-implementation period, then the resulting risk ratio and 95% confidence interval was not used to draw any conclusions because it is unreliable.

Table 2: Calculation of the 95% Confidence Interval for the Risk Ratio

	Post-implementation Period	Pre-implementation Period
Prescription met label requirement(s)	A	C
Prescription did *not* meet label requirement(s)	B	D
Total number of prescriptions	A+B	C+D

$$\text{Risk Ratio (RR)} = \frac{\frac{A}{A+B}}{\frac{C}{C+D}}$$

$$\log(RR) = \log\left(\frac{\frac{A}{A+B}}{\frac{C}{C+D}}\right)$$

$$Var(\log(RR)) = \left(\frac{\frac{B}{A}}{A+B}\right) + \left(\frac{\frac{D}{C}}{C+D}\right)$$

$$s.e.(\log(RR)) = \sqrt{\left(\frac{\frac{B}{A}}{A+B}\right) + \left(\frac{\frac{D}{C}}{C+D}\right)}$$

$$95\%\ CI = \exp\big(\log(RR) \pm 1.96 * s.e.(\log(RR))\big)$$

9.9.2.1.1. All Label Requirements

The rates for the primary endpoints of the study (and the proportion of all prescriptions that were consistent with the revised label) were 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). The 4 scenarios that were calculated are:

3. **Optimistic scenario.** Unknown indication assumed to be nausea and vomiting, duration assumed to be ≤7 days, and met the following conditions:
    a. Prescription for nausea and vomiting or unknown indication but no recent[a] diagnosis of GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease 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 medications (this considered such contraindicated co-medications only when they were prescribed prior to or on the date of the domperidone prescription).
4. **Intermediate scenario-A.** Unknown indication assumed to be an off-label indication, duration assumed to be ≤7 days, and met the following conditions:
    a. Prescription for nausea and vomiting but no recent[a] diagnosis of GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease patients, or as an aid to lactation. Unknown indication assumed to be off-label (this differed from #1).
    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 medications (this considered such contraindicated co-medications only when they were prescribed prior to or on the date of the domperidone prescription).
5. **Intermediate scenario-B.** Unknown indication assumed to be nausea and vomiting, duration assumed to be the days' supply, and met the following conditions:
    e. Prescription for nausea and vomiting or for unknown indication but no recent[a] diagnosis of GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease patients, or as an aid to lactation (this was the same as in #1);
    f. Duration (days' supply) ≤7 days (this differed from #1 and from #2, which did not examine days' supply);
    g. Dose no higher than recommended;
    h. No prescription to patients with certain cardiac and hepatic conditions; and
    i. No co-prescription with CYP3A4 inhibitors or QT-prolonging medications (this considered such contraindicated co-medications when prescribed prior to or on the date of the domperidone prescription or prescribed within the days potentially covered by the domperidone prescription).
6. **Pessimistic scenario.** Unknown indication assumed to be an off-label indication, duration assumed to be the days' supply, and met the following conditions:

[a] "Recent" defined as the two months up to and including the date of the domperidone prescription.

j. Prescription for nausea and vomiting but no recent[a] 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).

k. Duration (days' supply) ≤7 days (this differed from #1 and from #2, which did not examine days' supply);

l. Dose no higher than recommended;

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

n. No co-prescription with CYP3A4 inhibitors or QT-prolonging medications (this considered such contraindicated co-medications when prescribed prior to or on the date of the domperidone prescription or prescribed within the days potentially covered by the domperidone prescription).

9.9.2.2. Analysis of Secondary Objectives

The test statistic evaluated was the change in the proportion of all prescriptions that complied with each individual component of the composite endpoint during the 12 months before the label change (i.e., the pre-implementation period) versus the 12 months after the label change (i.e., the post-implementation period) as a measure of the effectiveness of the label change. This test statistic was evaluated as a risk ratio and presented separately for each component of the composite endpoint. The point estimate and 95% CI for the risk ratio are reported.

For example, for the maximum daily dose component of the composite endpoint, the risk ratio was the ratio of the proportion of domperidone prescriptions that met the maximum daily dose component of the composite endpoint between 1 April 2013 and 31 March 2014 (i.e., the pre-implementation period) and the proportion of prescriptions that met the maximum daily dose component of the composite endpoint between 1 October 2014 and 30 September 2015 (i.e., the post-implementation period).

Risk ratios were calculated and reported separately for each of the 4 remaining components of the composite endpoint:

- Prescribing for on-label indication;
  - Calculated under the following two scenarios (due to the uncertainty regarding unknown indications):
    - Unknown indication was assumed to be nausea and vomiting and therefore on-label; and
    - Unknown indication was assumed to be off-label.
- Duration of use (days' supply) ≤7 days;
- No concomitant use of medications that prolong the QT-interval or are potent CYP3A4 inhibitors;

[a] "Recent" defined as the two months up to and including the date of the domperidone prescription.

  - Calculated under the following two scenarios (due to the uncertainty regarding the duration of use of domperidone):
    - Those medications that were prescribed before or on the date of the domperidone prescription and whose duration of use included the date of the domperidone prescription (scenario where domperidone was used only for as little as 1 dose after it was prescribed); and
    - Those medications that were prescribed and/or had days' supply during the days' supply of the domperidone prescription (scenario where domperidone was used for the entire number of days' supplied).
- No prescribing to patients with contraindicated conditions, e.g., moderate or severe liver disease, underlying cardiac diseases.

The apparent indications and the days' supplied (≤7 days vs. >7 days) were tabulated for the pre- and post-implementation periods.

Sex and age were tabulated for the study cohorts for the pre-defined study periods.

All patients with an unknown age (i.e., both adult and paediatric patients) were reported in the tables for adults only.

9.9.3. Missing Values

Missing values were reported as missing and no imputation was undertaken.

9.9.4. Sensitivity Analyses

Sensitivity analyses were not included in the protocol because the study design examined 4 different scenarios that described different areas of uncertainty regarding domperidone use. Because the true scenario of use was genuinely not known, it was therefore difficult to identify a primary scenario and then conduct explicit sensitivity analyses as variations of that scenario. However, the four different scenarios served a similar purpose.

9.9.5. Amendments to the Statistical Analysis Plan

There were no amendments to the Statistical Analysis Plan.

9.10. Quality Control

QuintilesIMS confidentiality agreements are signed by all employees and include data protection and strict prohibitions on reidentification attempts. All aspects of the study were conducted within the framework of the QuintilesIMS Quality Management System. A Quality Control plan for the study was developed and executed. QuintilesIMS documented and retained a quality review of all final deliverables.

10. RESULTS

10.1. Participants and Treatment Information

The number of domperidone prescriptions and patients eligible for each analysis varied by analysis and by country and are reported in the Main Results section. The total number of

prescriptions and patients identified during the study period for each country are described in the following sections.

10.1.1. Belgium (Table 68, Table 69, Table 70)

In the QuintilesIMS EMR database Belgium, there were 53,575 adult domperidone prescriptions (N patients=37,098; Table 68); 9,949 paediatric domperidone prescriptions (N patients=7,704; Table 69); and 66 domperidone prescriptions filled by patients aged 12-14 years weighing less than 35 kg (N patients=54; Table 70) eligible for the analyses.

10.1.2. France (Table 71, Table 72, Table 73)

In the QuintilesIMS EMR database France, there were 324,213 adult domperidone prescriptions (N patients=194,118; Table 71); 75,465 paediatric domperidone prescriptions (N patients=56,764; Table 72); and 1,491 domperidone prescriptions filled by patients aged 12-14 years weighing less than 35 kg (N patients=1,160 patients; Table 73) eligible for the analyses.

10.1.3. Germany (Table 74, Table 75, Table 76)

In the QuintilesIMS Disease Analyzer Germany, there were 27,173 adult domperidone prescriptions (N patients=9,192; Table 74); 6 paediatric domperidone prescriptions (N patients=6; Table 75); and 1 domperidone prescription filled by patients aged 12-14 years weighing less than 35 kg (N patients=1; Table 76) eligible for the analyses.

10.1.4. Spain (Table 77, Table 78, Table 79)

In the QuintilesIMS EMR database Spain, there were 102,494 adult domperidone prescriptions (N patients=21,713; Table 77); 3,425 paediatric domperidone prescriptions (N patients=2,939; Table 78); and 49 domperidone prescriptions filled by patients aged 12-14 years weighing less than 35 kg (N patients=34; Table 79) eligible for the analyses.

10.1.5. United Kingdom (Table 80, Table 81, Table 82)

In the CPRD, there were 532,884 adult domperidone prescriptions (N patients=109,767; Table 80); 17,382 paediatric domperidone prescriptions (N patients=3,038; Table 81); and 141 domperidone prescriptions filled by patients aged 12-14 years weighing less than 35 kg (N patients=52; Table 82) eligible for the analyses.

10.2. Descriptive Data

Tables 3-17 display the demographics (age and sex) of patients receiving a domperidone prescription, overall and stratified by the pre-defined study periods. Results are presented separately for adult (≥12 years) and paediatric (<12 years) patients. The number and proportion of patients aged 12-14 with (1) a weight recorded during the study period and (2) a weight less than 35 kg are also reported.

Note: the sum of the "Entire Study Period" column may be greater than the number of unique patients in the entire study period. This is because patients can appear in more than one age group if they had >1 domperidone prescription in >1 pre-defined study period and they changed age groups. For example, if a patient was 17 years of age during the background period and then

was 21 years of age during the implementation period, they will be represented in both rows and in the appropriate time period for that row.

Note: the number of patients reported in each row of the "Entire Study Period" column is the number of unique patients for that row. If a patient received ≥1 domperidone prescription in ≥1 pre-defined study period, they are counted once in each pre-defined study period in which they have a prescription and once in the "Entire Study Period" for that row.

10.2.1. Belgium

Adult Patients (Table 3)

The largest proportion of adult patients receiving a domperidone prescription were aged 18-30 years (23.0%, N=8,533), followed by patients aged 31-40 years (17.0%, N=6,314), 41-50 years (16.0%, N=5,936), and 51-60 years (14.8%, N=5,489); the smallest proportion were aged >80 years (4.5%, N=1,670). There were more female adult patients (59.6%, N=22,115) who received a domperidone prescription than male adult patients (40.4%, N=14,983).

Paediatric Patients (Table 4)

Of the paediatric patients receiving a domperidone prescription, 69.5% (N=5,356) were aged 4-11 years and 33.0% (N=2,545) were aged 0-3 years. There were an approximately equal number of female and male paediatric patients who received a domperidone prescription (51.1% vs. 49.9%, female vs. male).

Patients Aged 12-14 Years (Table 5)

Of the 1,609 patients aged 12-14 years, 21.8% (N=351) had a weight recorded during the study period and 2.9% (N=46) weighed less than 35 kg.

10.2.2. France

Adult Patients (Table 6)

The largest proportion of adult patients receiving a domperidone prescription were aged 18-30 years (25.3%, N=49,072), followed by patients aged 31-40 years (17.9%, N=34,829), 41-50 years (15.6%, N=30,221), and 51-60 years (13.4%, N=26,107); the smallest proportion were aged >80 years (4.0%, N=7,781). There were more female adult patients (62.5%, N=121,262) who received a domperidone prescription than male adult patients (37.5%, N=72,849). Sex was unknown for 7 patients (0.0%).

Paediatric Patients (Table 7)

Of the paediatric patients receiving a domperidone prescription, 70.5% (N=40,045) were aged 4-11 years and 32.3% (N=18,309) were aged 0-3 years. There were an approximately equal number of female and male paediatric patients who received a domperidone prescription (49.5% vs. 50.4%, female vs. male). Sex was unknown for 4 paediatric patients (0.0%).

Patients Aged 12-14 Years (Table 8)

Of the 9,809 patients aged 12-14 years, 74.4% (N=7,297) had a weight recorded during the study period and 9.4% (N=918) weighed less than 35 kg.

10.2.3. Germany

Adult Patients (Table 9)

The largest proportion of adult patients receiving a domperidone prescription were aged 71-80 years (19.3%, N=1,777), followed by patients aged 18-30 years (15.1%, N=1,389), 61-70 years (15.0%, N=1,383), and 51-60 years (14.6%, N=1,341); the smallest proportion were aged 12-17 years (2.4%, N=223). There were 15 patients (0.2%) with an unknown age. There were more female adult patients (63.4%, N=5,832) who received a domperidone prescription than male adult patients (36.5%, N=3,355). Sex was unknown for 5 patients (0.1%).

Paediatric Patients (Table 10)

All 6 patients (100.0%) were aged 4-11 years; no patients were aged 0-3 years. There were more male paediatric patients (66.7%, N=4) who received a domperidone prescription than female paediatric patients (33.3%, N=2).

Patients Aged 12-14 Years (Table 11)

Of the 54 patients aged 12-14 years, 11.1% (N=6) had a weight recorded during the study period and 1.9% (N=1) weighed less than 35 kg.

10.2.4. Spain

Adult Patients (Table 12)

The largest proportion of adult patients receiving a domperidone prescription were aged 31-40 years (15.8%, N=3,347), followed by patients aged >80 years (15.1%, N=3,192), 18-30 years (14.4%, N=3,056), and 61-70 years (13.8%, N=2,919); the smallest proportion were aged 12-17 years (5.0%, N=1,059). There were more female adult patients (64.6%, N=13,671) who received a domperidone prescription than male adult patients (33.7%, N=7,143). Sex was unknown for 359 patients (1.7%).

Paediatric Patients (Table 13)

Of the paediatric patients receiving a domperidone prescription, 63.7% (N=1,873) were aged 4-11 years and 37.2% (N=1,094) were aged 0-3 years. There were an approximately equal number of female and male paediatric patients who received a domperidone prescription (47.1% vs. 51.5%, female vs. male). Sex was unknown for 42 paediatric patients (1.4%).

Patients Aged 12-14 Years (Table 14)

Of the 450 patients aged 12-14 years, 46.4% (N=209) had a weight recorded during the study period and 6.7% (N=30) weighed less than 35 kg.

10.2.5. United Kingdom

Adult Patients (Table 15)

The largest proportion of adult patients receiving a domperidone prescription were aged 61-70 years (18.4%, N=20,252), followed by patients aged 71-80 years (16.9%, N=18,557), 51-60 years (15.6%, N=17,174), and 41-50 years (14.2%, N=15,557); the smallest proportion were aged 12-17 years (3.1%, N=3,415). There were more female adult patients (67.7%, N=74,354) who received a domperidone prescription than male adult patients (32.3%, N=35,523).

Paediatric Patients (Table 16)

Of the paediatric patients receiving a domperidone prescription, 61.3% (N=1,836) were aged 4-11 years and 41.8% (N=1,252) were aged 0-3 years. There were an approximately equal number of female and male paediatric patients who received a domperidone prescription (47.1% vs. 52.9%, female vs. male).

Patients Aged 12-14 Years (Table 17)

Of the 1,250 patients aged 12-14 years, 31.6% (N=395) had a weight recorded during the study period and 5.8% (N=73) weighed less than 35 kg.

10.3. Outcome Data

Not applicable as no outcome data were collected.

10.4. Main Results

Tables 18, 22, 26, 28, 32, 36, 38, 42, 46, 48, 52, 56, 58, 62, and 66 report the number and proportion of domperidone prescriptions meeting *all* label requirements (also referred to as the composite endpoint) and the number of patients and rate of domperidone prescriptions per 1,000 domperidone-treated patients meeting *all* label requirements.

Tables 19, 23, 27, 29, 33, 37 39, 43, 47, 49, 53, 57, 59, 63, and 67 report the number and proportion of domperidone prescriptions meeting each *individual* label requirement and the number of patients and rate of domperidone prescriptions per 1,000 domperidone-treated patients meeting each *individual* label requirement.

Tables 20, 21, 24, 25, 30, 31, 34, 35, 40, 41, 44, 45, 50, 51, 54, 55, 60, 61, 64, and 65 report distributions of apparent indications and days' supplied (≤7 days vs. >7 days) for domperidone prescriptions across the pre-defined study periods. The number and proportion of prescriptions in each category and the rate per 1,000 domperidone-treated patients are reported by study period.

The RR of domperidone prescriptions meeting *all* label requirements and each *individual* label requirement, comparing the post-implementation period (numerator) to the pre-implementation period (denominator), by analysis scenario, is also presented.

Note: all RRs and comparisons are between the pre- and post-implementation periods only.

Note: all prescriptions classified with an unknown indication include prescriptions with no indication (i.e., the indication was missing or could not be estimated and thus was truly unknown) —and— prescriptions with indications for diagnoses *other than* nausea and vomiting, GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson patients, or as an aid to lactation (e.g., type 2 diabetes, acne, etc.).

Note: a prescription can correspond to more than one indication. Thus, the total number of prescriptions within a given study period column may add up to more than the corresponding total number of domperidone prescriptions.

Note: because some prescriptions contain missing information, the number of domperidone prescriptions and patients who received a domperidone prescription differs across the individual label requirements and by country. For example, if dose information was missing from a prescription, it was included in the on-label indication analyses, but not in the maximum daily dose analyses.

For more information about all label requirements, in the Variables section, see Composite endpoint/all label requirements.

For more information about the 4 scenarios in which the label requirements were analyzed, in the Statistical Methods section, see All label requirements.

For more information about how the on-label indication was assessed, in the Statistical Methods section, see Analysis of Secondary Objectives.

10.4.1. Belgium

Adult Patients (Table 18, Table 19, Table 20, Table 21)

Belgium showed small improvements in the proportion of domperidone prescriptions meeting all label requirements for the optimistic and intermediate scenario-A. No conclusions could be drawn for intermediate scenario-B or the pessimistic scenario due to the small proportions of prescriptions meeting all label requirements (Table 18).

Although the RRs showed nearly no change, Belgium demonstrated high compliance with the no concomitant use of contraindicated medications and no contraindicated conditions label requirements. There were small increases in the proportion of domperidone prescriptions complying with the maximum daily dose and on-label indication (where unknown/other indication was assumed off-label) label requirements. No conclusions could be drawn for the duration of use ≤7 days label requirement due to the small proportion of prescriptions meeting the label requirement (Table 19).

A majority of the domperidone prescriptions had an apparent indication for unknown or other (entire study period: 57.7%). The second most common indication was for nausea and vomiting (entire study period: 36.2%). The proportion of domperidone prescriptions prescribed off-label for GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease patients,

or as an aid to lactation did not exceed 5% during any of the pre-defined study periods (Table 20).

Paediatric Patients (Table 22, Table 23, Table 24, Table 25)

Sample size prohibited a robust analysis of the results; RRs for the 4 scenarios were either null (optimistic scenario and intermediate scenario-A) or could not be calculated due to the small proportions of prescriptions meeting all label requirements (intermediate scenario-B and the pessimistic scenario) (Table 22).

Although the RRs showed nearly no change, Belgium demonstrated high compliance with the no concomitant use of contraindicated medications, on-label indication (where unknown/other indication was assumed nausea and vomiting), and no contraindicated conditions label requirements; moderate compliance with the maximum daily dose label requirement; and low compliance with the on-label indication (where unknown/other indication was assumed off-label) label requirement. Compliance with the duration of use ≤7 days label requirement decreased substantially (Table 23).

A majority of the domperidone prescriptions had an apparent indication for unknown or other (entire study period: 64.0%). Nausea and vomiting (entire study period: 35.0%) was the second most common indication. The proportion of domperidone prescriptions prescribed for GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease patients, or as an aid to lactation did not exceed 2% during any of the pre-defined study periods (Table 24).

Patients Aged 12-14 Weighing Less Than 35 Kg (Table 26, Table 27)

Sample size prohibited a robust analysis of the results. The risk ratios for the 4 scenarios were either null (optimistic scenario) or could not be calculated due to small sample size (intermediate scenario-A, intermediate scenario-B, and the pessimistic scenario) (Table 26).

10.4.2. France

Adult Patients (Table 28, Table 29, Table 30, Table 31)

France showed large improvements across the optimistic scenario, intermediate scenario-A, and intermediate scenario-B. No conclusions could be drawn for the pessimistic scenario due to the small proportions of prescriptions meeting all label requirements (Table 28).

Although the RRs showed nearly no change, France demonstrated high compliance with the no concomitant use of contraindicated medications and no contraindicated conditions label requirements. There were large increases in the proportion of domperidone prescriptions complying with the maximum daily dose, duration of use ≤7 days, and on-label indication (where unknown/other was assumed nausea and vomiting and where unknown/other was assumed off-label) label requirements (Table 29).

A majority of the domperidone prescriptions had an apparent indication for unknown or other (entire study period: 64.5%). Nausea and vomiting was the second most common indication (entire study period: 18.0%). GERD was the third most common indication (entire study period:

13.9%). The proportion of domperidone prescriptions prescribed for gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease patients, or as an aid to lactation did not exceed 5% during any of the pre-defined study periods (Table 30).

Paediatric Patients (Table 32, Table 33, Table 34, Table 35)

France had a relatively robust sample size and showed large improvements in the proportion of domperidone prescriptions meeting all label requirements across all scenarios (Table 32).

Although the RRs showed nearly no change, France demonstrated high compliance with the on-label indication (where unknown/other indication was assumed nausea and vomiting), no concomitant use of contraindicated medications, and no contraindicated conditions label requirements. There were large increases in the proportion of domperidone prescriptions complying with the maximum daily dose and duration of use ≤7 days label requirements and a moderate increase in prescriptions complying with the on-label indication (where unknown/other indication was assumed off-label) label requirement (Table 33).

A majority of the domperidone prescriptions had an apparent indication for unknown or other (entire study period: 68.0%). Nausea and vomiting (entire study period: 30.2%) was the second most common indication. The proportion of domperidone prescriptions prescribed for GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease patients, or as an aid to lactation did not exceed 2% during any of the pre-defined study periods (Table 34).

Patients Aged 12-14 Weighing Less Than 35 Kg (Table 36, Table 37)

France had an adequate sample size and showed significant improvements in the proportion of domperidone prescriptions meeting all label requirements across all scenarios (Table 36).

Although the RRs showed nearly no change, France demonstrated high compliance with the on-label indication (where unknown/other indication was assumed nausea and vomiting), no concomitant use of contraindicated medications, and no contraindicated conditions label requirements and poor compliance with the on-label indication (other/unknown assumed off-label) label requirement. There were large increases in the proportion of domperidone prescriptions complying with the maximum daily dose and duration of use ≤7 days label requirements (Table 37).

10.4.3. Germany

Adult Patients (Table 38, Table 39, Table 40, Table 41)

Germany showed modest improvements across the optimistic scenario and intermediate scenario-B. No conclusions could be drawn for intermediate scenario-A and the pessimistic scenario due to the small proportions of prescriptions meeting all label requirements (Table 38).

Although the RRs showed nearly no change, Germany demonstrated high compliance with the no contraindicated conditions and no concomitant use of contraindicated medications label requirements. There was also very high compliance with the maximum daily dose label requirement, which increased very slightly. There was a large increase in the proportion of

domperidone prescriptions complying with the duration of use ≤7 days label requirement and a moderate increase in prescriptions complying with the on-label indication (where unknown/other was assumed nausea and vomiting) label requirement. Compliance with the on-label indication (where unknown/other was assumed off-label) label requirement decreased moderately (Table 39).

A majority of the domperidone prescriptions had an apparent indication for unknown or other (entire study period: 68.3%). The second most common indication was for GERD (entire study period: 15.6%). The proportion of domperidone prescriptions prescribed for nausea and vomiting, gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease patients, or as an aid to lactation did not exceed 9% during any of the pre-defined study periods (Table 40).

Paediatric Patients (Table 42, Table 43, Table 44, Table 45)

Sample size prohibited a robust analysis of the results, as only 6 paediatric domperidone prescription were recorded during the entire study period and no prescription had a recorded weight. As a result, no conclusions could be drawn from any scenario (Table 42).

Patients Aged 12-14 Weighing Less Than 35 Kg (Table 46, Table 47)

Sample size prohibited a robust analysis of the results, as only 1 prescription was recorded during the entire study period. As a result, the risk ratios for the 4 scenarios could not be calculated due to small sample size (Table 46).

10.4.4. Spain

Adult Patients (Table 48, Table 49, Table 50, Table 51)

Spain showed a small decline in the optimistic scenario. No conclusions could be drawn for intermediate scenario-A, intermediate scenario-B, or the pessimistic scenario due to the small proportions of prescriptions meeting all label requirements (Table 48).

Although the RR showed nearly no change, Spain demonstrated moderately high compliance with the no concomitant use of contraindicated medications label requirement. There was also high compliance for the proportion of domperidone prescriptions meeting the maximum daily dose label requirement, which increased very slightly, and the no contraindicated conditions label requirement, which decreased very slightly. There was also moderate compliance with the on-label indication (where unknown/other indication was assumed nausea and vomiting), which decreased slightly. No conclusions could be drawn for the on-label indication (where unknown/other indication was assumed off-label) and duration of use ≤7 days label requirements due to the small proportions of prescriptions meeting the label requirements (Table 49).

A majority of the domperidone prescriptions had an apparent indication for unknown or other (entire study period: 63.6%). The second most common indication was for gastroparesis (entire study period: 14.5%), followed by GERD (entire study period: 10.1%), and symptoms of postural hypotension in Parkinson's disease patients (entire study period: 9.9%). The proportion

of domperidone prescriptions prescribed for nausea and vomiting, IBS, or as an aid for lactation did not exceed 5% during any of the pre-defined study periods (Table 50).

Paediatric Patients (Table 52, Table 53, Table 54, Table 55)

Sample size prohibited a robust analysis of the results; no conclusion could be drawn from any scenario (Table 52).

Although the RRs showed nearly no change, Spain demonstrated high compliance with the duration of use ≤7 days, no concomitant use of contraindicated medications, and no contraindicated conditions label requirements and moderate compliance with the maximum daily dose label requirement. There were modest increases in the proportion of domperidone prescriptions complying with the on-label indication (where unknown/other indication assumed nausea and vomiting and where unknown/other) label requirement (Table 53).

A majority of the domperidone prescriptions had an apparent indication for unknown or other (entire study period: 74.9%). Nausea and vomiting was the second most common indication (entire study period: 16.4%) and GERD was the third most common indication (entire study period: 8.0%). The proportion of domperidone prescriptions prescribed for gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease patients, or as an aid to lactation did not exceed 2% during any of the pre-defined study periods (Table 54).

Patients Aged 12-14 Weighing Less Than 35 Kg (Table 56, Table 57)

Sample size prohibited a robust analysis of the results. There are no risk ratios to report since there were no domperidone prescriptions recorded during any pre-defined study period after the background period (Table 56).

10.4.5. United Kingdom

Adult Patients (Table 58, Table 59, Table 60, Table 61)

The UK showed a modest improvement for intermediate scenario-B and a small improvement for the optimistic scenario. No conclusions could be drawn for intermediate scenario-A and the pessimistic scenario due to the small proportions of prescriptions meeting all label requirements (Table 58).

Although the RRs showed nearly no change, the UK demonstrated high compliance with the no contraindicated conditions and no concomitant use of contraindicated medications label requirements. There was also high compliance with the on-label indication (where unknown/other indication was assumed nausea and vomiting) and maximum daily dose label requirements, which increased very slightly. There was a moderate increase in the proportion of domperidone prescriptions complying with the duration of use ≤7 days label requirement. No conclusion could be drawn for the on-label indication (where unknown/other indication was assumed off-label) due to the small proportions of prescriptions meeting the label requirements (Table 59).

A majority of the domperidone prescriptions had an apparent indication for unknown or other (entire study period: 89.5%). The proportion of domperidone prescriptions prescribed for nausea and vomiting, GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease patients, or as an aid to lactation did not exceed 5% during any of the pre-defined study periods (Table 60).

Paediatric Patients (Table 62, Table 63, Table 64, Table 65)

Sample size prohibited a robust analysis of the results. The RR for the optimistic scenario was null. No conclusions could be drawn for intermediate scenario-A, intermediate scenario-B, or the pessimistic scenario due to the small proportions of prescriptions meeting all label requirements (Table 62).

Although the RRs showed nearly no change, the UK demonstrated high compliance with the no contraindicated conditions, on-label indication (where unknown/other indication was assumed nausea and vomiting), and no concomitant use of contraindicated medications label requirements; and low-to-moderate compliance with the maximum daily dose label requirement. No conclusions could be drawn for the on-label indication (where unknown/other indication was assumed off-label) and duration of use ≤7 days label requirements due to the small proportions of prescriptions meeting the label requirements (Table 63).

A majority of the domperidone prescriptions had an apparent indication for unknown or other (entire study period: 88.3%). The proportion of domperidone prescriptions prescribed for nausea and vomiting, GERD, gastroparesis, IBS, symptoms of postural hypotension in Parkinson's disease patients, or as an aid to lactation did not exceed 8% during any of the pre-defined study periods (Table 64).

Patients Aged 12-14 Weighing Less Than 35 Kg (Table 66, Table 67)

Sample size prohibited a robust analysis of the results. The risk ratios for the 4 scenarios were either null or could not be calculated due to the small proportions of prescriptions meeting all label requirements (Table 66).

10.5. Other Analyses

Tables 68-82 summarize missing domperidone prescription data on duration and daily dose for the study period at the prescription level and at the patient level. Data were considered missing if they were not included in the prescription and dose or duration could not be calculated from other available data. A summary of missing weight data for paediatric patients also is provided. In addition to the summaries for adult and paediatric patients, this series also provides summaries for patients, 12-14 years of age who are less than 35 kg.

Note: patients in these tables can have ≥1 prescription and, thus, may be counted as having ≥1 prescription with complete data ***and*** as having ≥1 prescription with missing data. Thus, proportions could add up to more than 100.0%.

Note: The patient and prescription counts in Tables 80-82 for the UK are based on age at index (i.e., a patient's a first domperidone prescription during the study period) as opposed to age at event (i.e., each qualifying domperidone prescription for a patient). All other tables summarizing missing domperidone prescription data use age at event.

The proportion of adult prescriptions without a recorded duration (and that could not be calculated using other information from the prescription) was moderately high for Spain (33.7%; Table 77) and the UK (30.4%; Table 80). The proportion of adult prescriptions without a recorded daily dose (and that could not be calculated using other information from the prescription) was moderately high for Spain (27.9%) and the UK (30.4%).

The proportion of prescriptions without a recorded weight for children aged <12 years ranged from 13.4% (France; Table 72) to 100.0% (Germany; Table 75). The proportion of paediatric prescriptions without a recorded duration (and that could not be calculated using other information from the prescription) was high for Belgium (62.1%; Table 69), Spain (91.2%; Table 78), and the UK (63.9%; Table 81) and moderate for France (25.0%). The proportion of paediatric prescriptions without a recorded daily dose (and that could not be calculated using other information from the prescription) was high for Belgium (79.6%), Spain (61.8%), and the UK (63.9%).

For patients aged 12-14 years weighing less than 35 kg, the proportion of prescriptions without a recorded duration (and that could not be calculated using other information from the prescription) was very high for Spain (95.9%; Table 79) and moderate for Belgium (25.8%; Table 70) and the UK (42.6%; Table 82). For patients aged 12-14 years weighing less than 35 kg, the proportion of prescriptions without a recorded daily dose (and that could not be calculated using other information from the prescription) was moderate for Spain (32.7%) and the UK (42.6%).

10.6. Adverse Events/Adverse Reactions

There were no adverse events/adverse reactions to report.

11. DISCUSSION

11.1. Key Results

11.1.1. Adult Patients

Overall, the results varied by scenario and country. For the optimistic scenario, a moderate improvement in compliance with all label requirements was observed for most countries, with the exception of France, which demonstrated a large improvement. Most countries had high compliance with the label requirements for no contraindicated medications and no contraindicated conditions and moderate to high compliance with the maximum daily dose label requirement. It is important to note that for the proportions of domperidone prescriptions complying with these 3 label requirements, compliance was high or moderately high across all study periods. The notable exception to this, however, was France, which dramatically improved compliance with the maximum daily dose label requirement in the post-implementation period.

Therefore, to see an improvement in compliance with all label requirements under the optimistic scenario, we would have to have seen an appreciable increase in the number of prescriptions with an indication recorded as either nausea and vomiting or unknown (e.g., France, Germany) and/or an increase in the number of prescriptions meeting the maximum daily dose label requirements (e.g., France). Because duration of use was always assumed to be ≤7 days in the optimistic scenario, any improvements in compliance with this particular label requirement were not reflected in the RRs.

The findings for intermediate scenario-A were inconclusive. Risk ratios ranged from a small improvement in compliance (Belgium) to a large improvement in compliance (France), however, no conclusions could be drawn for Germany, Spain, or the UK due to the small proportions of prescriptions meeting all label requirements. Intermediate scenario-A was defined in a similar manner as the optimistic scenario, however, unknown indications were classified as off-label. Therefore, to see an improvement in the compliance with all label requirements under intermediate scenario-A, we would have to have seen an appreciable increase in the number of prescriptions with an indication recorded as nausea and vomiting (e.g., Belgium, France) and/or an increase in the number of prescriptions meeting the maximum daily dose label requirements (e.g., France).

The findings for intermediate scenario-B were mostly positive and ranged from a modest improvement in compliance (UK) to a large improvement in compliance (France, Germany), however, no conclusions could be drawn for Belgium or Spain due to the small proportions of prescriptions meeting all label requirements. Intermediate scenario-B was defined in a similar manner as the optimistic scenario, however, duration of use was set equal to the days' supply as written on the prescription. Therefore, to see an improvement in the compliance with all label requirements under intermediate scenario-B, we would have to have seen an appreciable increase in the number of prescriptions with an indication recorded as either nausea and vomiting or unknown (e.g., France, Germany) and/or an increase in the number of prescriptions with a recorded days' supply ≤7 days (e.g., France, UK) and/or an increase in the number of prescriptions meeting the maximum daily dose (e.g., France) label requirements.

The findings for the pessimistic scenario were inconclusive due to the small proportions of prescriptions in all countries meeting all label requirements. The pessimistic scenario differed from the optimistic scenario in 2 important ways: (1) unknown indications were assumed to be off-label and (2) duration of use was set equal to the days' supply as written on the prescription. Therefore, to see an improvement in the compliance with all label requirements under the pessimistic scenario, we would have to have seen an appreciable increase in the number of prescriptions with an indication recorded as nausea and vomiting (e.g., Belgium, France) and/or an increase in the number of prescriptions with a recorded days' supply ≤7 days (e.g., France, UK) and/or an increase in the number of prescriptions meeting the maximum daily dose (e.g., France) label requirements.

11.1.2. Paediatric Patients

Sample size prohibited a robust analysis of the results for the paediatric patients. Risk ratios for the 4 scenarios either were null, could not be calculated due to 0 domperidone prescriptions being recorded in the pre- and/or post-implementation periods, or no conclusions could be drawn due to the small proportions of prescriptions meeting all label requirements. The exception to this was France, which had a relatively robust paediatric sample and showed large improvements in the proportion of domperidone prescriptions meeting all label requirements across all scenarios. These results were primarily driven by improvements in compliance with the duration of use ≤7 days, maximum daily dose, and on-label indication (where unknown/other indication was assumed off-label) label requirements.

11.1.3. Patients Aged 12-14 Years Weighing Less Than 35 Kg

Sample size prohibited a robust analysis of the results for the patients aged 12-14 years weighing less than 35 kg. Risk ratios for the 4 scenarios either were null, could not be calculated due to 0 domperidone prescriptions being recorded in the pre- and/or post-implementation periods, or no conclusions could be drawn due to the small proportions of prescriptions meeting all label requirements. The exception to this was France, which had a modest sample of patients aged 12-14 years weighing less than 35 kg and showed large improvements in the proportion of domperidone prescriptions meeting all label requirements across all scenarios. These results were primarily driven by improvements in compliance with the duration of use ≤7 days and maximum daily dose label requirements.

11.2. Limitations

There are two major limitations of this study. First, the information required to identify the indication for a domperidone prescription and classify it as nausea/vomiting or other was often missing; and second, the databases specified days' supply rather than days of use but, for the reasons considered in the Interpretation section, days' supply could be greater than days of use. This created uncertainty about compliance with the limitation on duration of use.

Other limitations of this study include:

- The databases provided detailed information on prescribed medications but not on the actual use of the medications by patients. This may specifically be a limitation for drugs that are used PRN (pro re nata; when necessary), such as domperidone. Thus, depending on whether a patient decided to take or not take domperidone on a particular day, patients may be classified as exposed when they are not actually taking the drug or unexposed when they are actually taking the drug.
- In these databases, prescriptions were not always explicitly linked to diagnoses. Only Belgium, France, and Spain had an indication field that was explicitly associated with the prescription. The indication for which the drug was prescribed was deduced from the list of diagnoses documented in the patient's records on or shortly before the day of the prescription. Since a substantial proportion of prescriptions did not either have a diagnosis or have a diagnosis that was plausible as an indication, there was appreciable uncertainty about the indications for which the medication was prescribed.

- While patients did have a unique ID within the same practice, this unique ID did not follow them when they were seen at an outside practice. As a consequence, we could not identify patients who received care at multiple practices. Thus, patients could have seen multiple providers and data from all of those providers that they visited might not have been included in the database. Therefore, some diagnoses and concurrent use with contraindicated medications were missed and may be underestimated in this study.
- In the Disease Analyzer (Germany), the recommended daily dose was most often provided the first time the physician prescribed the medication or when there was a dosage change. If a dose was not recorded with the first prescription, dose was recorded as unknown until the physician entered a dose.
- Missing days supplied (used as a proxy for duration of use) and daily dose was quite high for some countries.
- Some of the confidence intervals reported are unstable due to small sample size, the small number of domperidone prescriptions in the numerator of the proportions giving rise to the RRs, and/or the small proportions of domperidone prescriptions in either the numerator and/or denominator of the RR itself.
- The 4 scenarios took an "all or nothing" approach in labeling duration or an unknown indication as on or off-label that most likely did not reflect the true usage of domperidone in the study population.

11.3. Interpretation

This report presents the results of a domperidone drug utilisation study for the outpatient setting in 5 EU countries based on longitudinal patient-level databases. Due to uncertainty regarding (1) indication and (2) duration of use (which might have been shorter than the days' supply due to domperidone being used PRN), it was decided *a priori* to evaluate the proportion of domperidone prescriptions meeting all label requirements before and after the implementation of the risk minimisation measures under 4 different scenarios, which made different assumptions about whether an unknown indication or duration of use was on- or off-label. It was reasoned that the "truth" of how domperidone was being prescribed and used (in terms of these two parameters) would be bracketed by the results from the 4 scenarios reported.
The results showed that most of the domperidone prescriptions had an indication for unknown or other diagnoses. This was most likely due to the fact that healthcare providers do not regularly enter indication for prescriptions or ensure that indication is entered correctly (Belgium, France, and Spain) and that the Germany and UK data sources do not have an indication field explicitly associated with the prescription. Therefore, indication was unknown for a large percentage of domperidone prescriptions and our 4 scenarios either overestimated (optimistic scenario, intermediate scenario-B) or underestimated (intermediate scenario-A, pessimistic scenario) compliance with the on-label indication label requirement as a result of the "all or nothing" approach to classifying prescriptions with an unknown or other indication as either all on-label (i.e., all with a nausea and vomiting indication) or all off-label.

In addition, most of the domperidone prescriptions had a days' supply >7 days. It is possible that this is the result of how medications are packaged and dispensed and/or reimbursed in the 5 countries[a]. For example, it is possible that a healthcare provider in Belgium knew that a pack size of domperidone was 30 tablets and therefore prescribed 30 tablets instead of 21 tablets (or fewer to comply with the label's limitation on days' supply). Furthermore, since domperidone is used PRN, it is possible that some healthcare providers prescribed extra doses for future use. Additionally, in some countries, the cost to the patient of a 30 days' supply was identical to the cost of a 7 days' supply. Therefore, actual duration of use was truly unknown for a large percentage of domperidone prescriptions and our 4 scenarios either overestimated (optimistic scenario, intermediate scenario-A) or underestimated (intermediate scenario-B, pessimistic scenario) compliance with the duration of use ≤7 days label requirement as a result of the "all or nothing" approach to classifying duration of use in the different scenarios.

Nonetheless, France had the most robust findings of all the countries and showed improvements in complying with all label-requirements from the pre- to the post-implementation period across all scenarios for adults, paediatrics, and patients aged 12-14 years weighing less than 35 kg. This suggests that the risk minimisation measures may have had an impact on the off-labeling prescribing of domperidone. Or it could be the result of the risk minimisation measures implemented in combination with the effect of a recently published study that found adverse cardiac events associated with domperidone use in the French population and inappropriate domperidone prescribing in paediatric patients.[1]

The results for Germany and the UK were inconclusive. The optimistic scenario and intermediate scenario-B showed improvements, however, no conclusions could be drawn for intermediate scenario-A and the pessimistic scenario. Therefore, it is possible that the risk minimisation measures had an impact on off-label prescribing of domperidone in these 2 countries. A prospective study conducted in 2016 found that following the publication of The Medicines and Healthcare Regulatory Agency recommendations restricting domperidone use in the UK, there was a significant reduction in the number of patients treated with domperidone and concomitant usage of drugs known to prolong the QTc interval.[3]

Belgium's results were also inconclusive. The optimistic scenario and intermediate scenario-A showed improvements, however, no conclusions could be drawn for intermediate scenario-B and the pessimistic scenario. Therefore, it is possible that the risk minimisation measures had an impact on off-labeling prescribing of domperidone in Belgium, however, the impact was minimal.

[a] For example, in Belgium, package sizes range from 1-100 tablets, 1-200 mL (oral solution), and 1-6 suppositories. In France, package sizes range from 1-40 tablets and 1-200 mL (oral solution). In Germany, package sizes range from 1-100 tablets (which are *not* split) and 30-100 mL (oral solution). In Spain, package size range from 1-30 tablets and 200 mL (oral solution). Finally, in the UK, packages sizes range from 10-100 tablets (which can be split), 1-10 suppositories, and 200 mL (oral solution) (Janssen PRD, personal communication, 12-SEP-2017).

Spain's results suggest that the risk minimisation measures did not have an impact on off-label prescribing of domperidone in Spain. There was a decrease in compliance with all label requirements under the optimistic scenario and no conclusions could be drawn for intermediate scenarios-A and B, and the pessimistic scenario. This may be due to the lack of impact of safety warnings in Spain: a study conducted in Spain looking at changes in systemic use of piroxicam use after a safety warning was issued about its risk found that population exposure to systemic use of piroxicam remained unchanged after the safety warning and only declined sharply after the introduction of prior authorisation.[2]

Previous studies have shown mixed results of safety-related regulatory action on drug utilisation. A systematic review of 52 studies by Piening et al. (2012) looking at the impact of safety warnings on clinical practice across multiple countries (including countries in the EU and the United States) found that intended effects of safety warnings were found in most cases, yet varied between drug groups, and that unintended effects of safety warnings were also reported.[5] Overall, 56% of the analyses reported intended effects, 27% reported no effects, and 17% reported an effect for one outcome measure but no effect for another. The interrupted time series studies reported more mixed findings (41% intended impact; 41% mixed impact) than the before/after studies (72% intended; 8% mixed impact). However, there are inherent methodological flaws in before/after studies that should be considered.[7] Selective serotonin reuptake inhibitors, third-generation oral contraceptives, and cisapride were the 3 main drug groups assessed in the review. While domperidone was not assessed in the study, the cisapride findings might be most relevant due to the similar safety warnings that both drugs received (i.e., cardiac arrhythmias/prolonged QT interval, with concurrent CYP3A4 inhibitor use). There were mixed effects for the cisapride safety warnings evaluated in the 5 interrupted time series analyses and mostly no effects in the 4 before/after studies.

Piening et al. (2012) also looked at the impact of DHPCs on drug utilisation for new users of 46 drugs in the Netherlands and found that while there were substantial short- and long-term decreases in use, they only occurred in approximately half and a third of DHPCs, respectively.[6]

Another study conducted in the Netherlands looked at the effect of a DHPC letter on the concomitant use of clopidogrel and proton pump inhibitors and found that while the advice of the regulators was followed, it was done so reluctantly and not fully (partly, the authors hypothesized, as a result of the doubt surrounding the interaction between the two medications).[4] A similar study conducted in the UK, also looking at concomitant use of clopidogrel and proton pump inhibitors, found that a DHPC letter was associated with changes in prescribing practices, however, the impact was variable depending on the intervention described by the warning.[8]

In summary, there is inconsistent data in the literature to support the effectiveness of safety warnings and DHPC letters on changing prescribing behavior. In this study, with the exception of France, the results suggest that the risk minimisation measures had a very modest effect on the off-label prescribing of domperidone. However, these results should be interpreted in the context that true duration of use and true indication were not known for a large percentage of domperidone prescriptions. That is, a large proportion of domperidone prescriptions had an unknown or other indication and/or >7 days' supply and while the study design addressed the

uncertainty by analyzing utilisation under 4 scenarios, there was much heterogeneity of results and results were not always robust. Reasons include, but are not limited to, limitations in the secondary data sources and small sample size.

11.4. Generalisability

This drug utilisation study presents results on the use of domperidone in the outpatient setting in 5 European countries based on data from large patient-level EMR databases. There were minimal restrictions to the study population and thus there were minimal effects on the external validity of study results. The countries were selected to include some with relatively high per capita use of domperidone and at least 1 country with relatively low per capita use of domperidone, as well as based on the availability of robust longitudinal EMR databases in each country. The selected EMR data sources for this study were designed to be representative for Belgium, France, Spain, Germany, and the UK. Taking into account the known limitations of the databases, the findings are considered generalisable to the countries where the study was conducted, however, the results may not generalise across countries.

For Belgium, France, and the UK, data came from GP providers only and included both adult and paediatric patients. In Spain and Germany, data came from both GP providers and Paediatric providers. Because the data are primarily from GPs, utilisation patterns from specialists may differ.

12. OTHER INFORMATION

There is no other information to address.

13. CONCLUSION

Overall, it was difficult to draw any conclusions regarding the effect of the risk minimisation measures on compliance with on-label prescribing of domperidone, with the possible exception of the results for France, which showed improvements across most scenarios for all patient populations. For the other countries, however, a significant number of domperidone prescriptions were missing data for indication and/or duration of use due to the limitations associated with the secondary data sources. Therefore, our ability to approximate the truth of how domperidone was prescribed via the 4 scenarios was limited. Sample size prohibited drawing any conclusions for the paediatric patients in Belgium, Germany, Spain, and the UK.

14. REFERENCES

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ANNEX 1: STAND-ALONE DOCUMENTS

The following appendices are either included with the report or are available on request.

1 Protocol and Amendments

2 Sample Case Report Form(s) (Not Applicable)

3 List of IECs or IRBs and Sample Consent Forms

4 List and Description of Investigators and Sites (Not Applicable)

5 Signature of Sponsor's Responsible Medical Officer (located at the end of this document)
Signature of Principal or Coordinating Investigator(s)

6 Listing of Patients Receiving Test Drug(s) from Specified Batch (Not Applicable)

7 Randomization Scheme (Not Applicable)

8 Audit Certificates (Not Applicable)

9 Documentation of Statistical Methods and Interim Analysis Plans

10 Documentation of Interlaboratory Standardization Methods and Quality Assurance Procedures if Used (Not Applicable)

11 Publications Based on the Study (Not Applicable)

12 Important Publications Referenced in the Report

13 Data Listings (Not Applicable)

SIGNATURE OF SPONSOR'S RESPONSIBLE MEDICAL OFFICER

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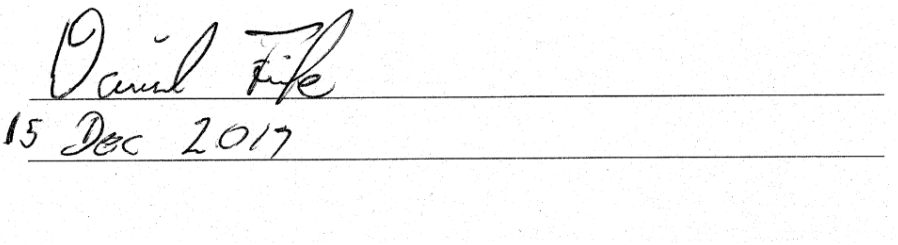
I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE: 

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