Janssen Research and Development*
on behalf of the Domperidone DUS Collaboration Group

Non-interventional Post Authorization Safety Study – Study Report

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A Post-Authorisation Safety Study (PASS) to Assess the Effectiveness of the Risk Minimisation Measures of Domperidone – Physician Survey

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Protocol RRA-17004

Motilium® Domperidone

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EU PAS Register Number: EUPAS16095

PRINCIPAL INVESTIGATOR: Mr Gavin Taylor-Stokes, MBA – Adelphi Real World Ltd, Bollington, Cheshire; UK

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: Dr Richarz Ute, Janssen Global Services, Gubelstrasse 34, Zug, Switzerland

DATE STUDY INITIATED: 04 January 2017

DATE STUDY COMPLETED: 31 March 2017

PASS INFORMATION

Title:	A Post-Authorisation Safety Study (PASS) to Assess the Effectiveness of the Risk Minimisation Measures of Domperidone – Physician Survey
Version identifier of the final study report:	1.0
Date of last version of the protocol:	01 March 2016
EU PAS Register No:	EUPAS16095
Active substance (INN common name):	Domperidone
Pharmacotherapeutic group (ATC Code):	A03F A03
Medicinal product(s):	Domperidone
Product reference:	ATC code:A03FA03
Procedure number:	EMEA/H/N/PSP/J/0016.1
Name of Marketing Authorization Holder(s)	Janssen Research & Development on behalf of the Domperidone DUS Collaboration Group (a group of all MAHs involved in the Consortium can be found in section 4: OTHER RESPONSIBLE PARTIES)
Joint PASS	Yes
Research question and objectives	The primary objective of the study is to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the change in SmPC and the distribution of DHPC.
Country(-ies) of study	France, Germany, the United Kingdom, Belgium, and Spain
Author	The DUS protocol subcommittee of the Domperidone DUS Collaboration Group

Status:	Approved
CSR Version:	1.0
Version Date:	13 June 2017
Prepared by:	Janssen Research and Development on behalf of the Domperidone DUS Collaboration Group
EDMS number:	EDMS-ERI-144396452:2.0

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

MARKETING AUTHORIZATION HOLDER(S)

Name of Marketing Authorization Holder:	Janssen Research & Development on behalf of the Domperidone DUS Collaboration Group
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A complete list of Marketing Authorisation Holders can be found in section 4: OTHER RESPONSIBLE PARTIES

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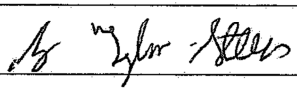
Signature:	
Date:	15TH JUNE 2017

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1. ABSTRACT

Name of Sponsor/Company	Janssen Research and Development on behalf of the Domperidone DUS Collaboration Group
Name of Finished Product	Domperidone

Protocol No.: RRA-17004

Title of Study: A Post-Authorisation Safety Study (PASS) to Assess the Effectiveness of the Risk Minimisation Measures of Domperidone (v1.0, 28 April 2017), Physician Survey

Sponsor's Responsible Medical Officer: Dr Ute Richarz **(Main Author)**

Keywords: domperidone, PASS, DUS, prescribers

EU PAS Register Number: EUPAS16095

Marketing Authorization Holder(s): Domperidone DUS Collaboration Group (for full membership, please refer to section 4: OTHER RESPONSIBLE PARTIES

Names and Affiliations of Principal Investigator(s): Gavin Taylor-Stokes, MBA – Adelphi Real World Ltd, Bollington, Cheshire; UK

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

Study Period: 04 January 2017 – 31 March 2017

Background and Rationale: In March 2013, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) initiated a review of domperidone-containing medicines at the request of the Federal Agency for Medicines and Health Products (FAMHP), under Article 31 of Directive 2001/83/EC over concerns about cardiac adverse effects of domperidone. Subsequently, the PRAC recommended that the product label (Summary of Product Characteristics [SmPC] and Patient Information Leaflet[PIL]) of domperidone-containing medicines be updated and considered that a Direct Healthcare Professional Communication (DHPC) was needed to raise awareness of the new recommendations in the product information and other risk minimisation measures.

The PRAC also recommended Drug Utilisation Study (DUS) should be conducted to assess the effectiveness of risk minimization measures and to monitor off-label use. Market authorisation holders (MAHs) concerned by this condition were strongly encouraged to work together on the protocols and conduct of the DUS. As such, the DUS study has been conducted as a joint effort of MAHs who agreed to participate in the consortium for domperidone. The present study aims to describe prescriber understanding, knowledge and awareness of the new safety information on domperidone, whilst a separate retrospective database study is being conducted to describe prescribing patterns and the extent to which they comply with the label.

Research Question and Objectives: Primary objective:

The primary objective of the study was to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the change in SmPC and the distribution of the DHPC, including: indications for domperidone prescribing, length of treatment, maximum daily dose, concomitant use of domperidone and other drugs known to prolong QT-interval or potent CYP3A4 inhibitors, contraindicated conditions and treated population characteristics.

Study Design: This was a multi-national, non-interventional cross-sectional study. A physician survey was developed and administered in a group of prescribers to assess the awareness and level of

understanding and knowledge regarding the new safety information for domperidone following the change in the SmPC and the distribution of DHPC. The study was implemented across 5 EU countries with considered to have significant prescription rates per population: Belgium, France, Germany, Spain and the United Kingdom. Data for the survey was collected electronically via the internet.

Setting: Physicians were identified from a market research database of Health Care Providers. Email notifications were sent out to physicians in 5 areas of medicine (see 'Patient Population and study size'). The fieldwork lasted for a period of 3 months and reminder emails were sent twice a week. Data collection was conducted through use of an online survey. Participating physicians accessed the survey by clicking on a link within the email and qualified for inclusion via screening questions.

Population and Study Size: The study population comprised of health practitioners specialised in the following 5 areas of medicine: primary care practice (PCP, general practice and internal medicine), gastroenterology, paediatrics, obstetrics/gynaecology and neurology. These specialities where chosen because they were expected to prescribe domperidone more regularly on label. The latter two specialities of prescribers were chosen for their potential to prescribe domperidone more frequently for the approved label or off-label indications.

Across all countries the quota was met for the PCP, gastroenterologist and neurologist specialities with a total of 1,380 completed surveys (900/900 PCPs, 240/240 gastroenterologists, 240/240 neurologists). Conversely, the quota was not met for the obstetrician/gynaecologist and paediatrician specialities with a total of 425 completed surveys (200/250 obstetricians/gynaecologists, 225/250 paediatricians). This was 75 less than the quotas.

Variables and Data Sources: The primary study endpoint was the physician knowledge and understanding of the new safety information for domperidone, as detailed in the SmPC and DHPC. The operational definitions of the study endpoints included evaluations of indications for domperidone prescribing, length of treatment, maximum daily dose, concomitant use of domperidone, contraindicated conditions, and treated population characteristics. An additional variable captured was the prescribing behaviour of domperidone for off-label indications. In addition, prescriber characteristic data were collected including age, sex, speciality, clinical practice type, and country. The survey was conducted using a multiple choice survey (see Appendix C of the protocol) via the internet to address the most important safety information in the DHPC and potential off-label use. The survey was translated into the local language in each country.

Statistical Methods: Descriptive statistics are presented for evaluation and comparison of prescriber knowledge and awareness as measured by the study survey. The study population is described using the demographic characteristics age, sex, speciality, clinical practice type, and country. Continuous variables are reported using appropriate descriptive statistics, such as mean, median, standard deviation and range. Categorical variables are described using frequencies. As per the protocol (Protocol - RRA-17004) point estimate and 95% confidence interval (CI) of percent of HCPs with correct responses to each question are presented. The primary analysis presents the rate of correct answers for all countries pooled together. The secondary analysis presents the rates of correct answers by country. Further stratification by baseline variables were performed as described in the statistical analysis plan.

Results: The majority of responding physicians were able to correctly identify the approved indication of domperidone ('Nausea and Vomiting' – 80% correct), the maximum recommended duration of use ('7 days' – 70% correct) and the maximum daily dose for adults ('30 mg per day (10 mg TID (three times daily))' 84%). Across all countries answers were similar. Overall, 21% of responding physicians stated they did not readily know the dosing requirements in adults but of these responding physicians, most had access to a prescribing guide (86%). The majority of those without access to a prescribing guide (69%) were still able to correctly identify the maximum daily dose for adults. Thus <1% of the total sample of responding physicians did not have access to a prescribing guide and also did not know the maximum daily dose for adults.

Just over a third of physicians (37%) could identify the correct maximum dose for neonates, infants and adolescents however; the gap in knowledge was more marked in responding physicians who were unable to refer to a prescribing guide (22%).

A high proportion of responding physicians (87%) could correctly identify 'Drugs that prolong the QT interval' as a contraindication for domperidone with a more moderate proportion (37%) identifying 'Drugs that are potent CYP3A4 inhibitors' as a correct response. Responding physicians selected one of the correct answers in the majority of cases (85%) but a lower proportion identified both together (26%).

Again, a high proportion of responding physicians (87%) could correctly identify 'Prolongation of cardiac conduction intervals, particularly QTc' as a disease contraindicated for domperidone, with lower levels (48%) correctly identifying 'Moderate to severe hepatic impairment' as a contraindication. Despite these high levels of awareness only 4% identified these two contraindications alone without various other incorrect responses being selected as well. Finally, 17% of responding physicians were unable to correctly identify that domperidone should be prescribed for 'Relief of the symptoms of nausea and vomiting' in view of the revised label.

Adverse Events/Adverse reactions: No adverse events were reported.

Discussion: The results highlight high levels of awareness for the updated label of domperidone containing products. Large proportions of physicians (>80%) were aware of indications of use, maximum dose duration, maximum dose in adults and concomitant use of domperidone.

However, more moderate to lower awareness was seen with regards to maximum daily dose in children and neonates and contraindications of domperidone. Whilst the survey was able to measure physician awareness of the domperidone label at time of survey completion, it should be noted that there was a two-year period between delivery of the DHPC and conducting of the survey. Therefore, it is likely that physicians cannot recall all the information provided in the DHPC. It is unclear what constitutes an acceptable time period to assess recall of the DHPC and no previous data was available on the baseline physician knowledge prior to the DHPC. An additional database study is being conducted to complement the survey. This study will provide data on prescribing patterns and the extent of off-label use of domperidone. These results will need to be considered in conjunction with the current survey data before possible actions can be agreed upon.

Additionally, it was observed that obstetricians/gynaecologists and paediatricians are low prescribers of domperidone. In total, 318 and 210 physicians (obstetricians/gynaecologists and paediatricians respectively) screened out at Part II of the study survey, suggesting that these physicians represent low prescribing groups. As a result of the high level of screen outs, the quota for both these specialities was not met.

Data collected demonstrated that whilst respondents and non-respondents were still more likely to be male, this was significantly less pronounced in the non-respondents group. Non-responding physicians were most likely to be PCPs and were not significantly different than responding physicians with regards to the time they practice medicine. The pattern of non-responding physicians primary setting (i.e., setting they practiced in the most) was similar across all countries with an 'all office/clinic' setting being most common in both responding and non-responding physicians.

Conclusions: Responding physicians demonstrated a high level of knowledge on the recommended changes to the domperidone label. Overall, there was a high level of access to prescribing guide; most responding physicians recalled receiving the information and demonstrated working knowledge of the revised/updated product limitations of the indication, dose administration duration, maximum dose and concomitant use of domperidone, though high awareness was observed for concomitant use of domperidone in drugs that prolong the QT interval.

However, the results highlight a limited awareness on:

- the daily doses in infants and neonates and the contraindications of the drug and the reduction in maximum daily dose in children and neonates to 0.25 mg TID as per the recent update in label indication (and so as responding physicians were largely unable to correctly identify this change). Physicians largely selected a lower than recommended dose, perhaps highlighting prudent behaviour in light of limited awareness.

- the right set of contraindications (and so as whilst a majority of responding physicians was able to correctly identify contraindications, they were not able to do so without identifying further incorrect ones).

The findings from this survey will be complemented with those from the database study exploring prescribing patterns and off-label use of domperidone. Possible actions of both studies should be considered in conjunction following completion of the database study in Q4 of 2017.

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADR	adverse drug reaction
AE	adverse event
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures - human
CRO	contract research organisation
DHPC	Direct Healthcare Professional Communication
DUS	Drug Utilisation Study
EMA	European Medicines agency
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
GERD	gastro-oesophageal reflux disease
HCP	Health Care Provider
MAH	Marketing Authorisation Holder
IEC	Independent Ethics Committee
PASS	Post-authorisation Safety Study
PCP	primary care provider
PhVWP	Pharmacovigilance Working Party
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
SmPC	Summary of Product Characteristics
TID	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.
Post Authorization 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: Gavin Taylor-Stokes, MBA

Coordinating Investigator: Not Applicable

4. OTHER RESPONSIBLE PARTIES

A list of all parties to the consortium and their market authorisation holder affiliates can be found below.

The contact details for each of the parties involved are available in Annex 2.

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 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	

Party **(*: Party itself does not hold a MA)**	**MAH Affiliates**
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
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	

Sponsor's Responsible:	
Medical Officer:	*Ute Richarz, MD
Statistician:	*Peter Hu, PhD
Contract Research Organization and level of involvement:	Adelphi Real World Ltd – Data collection, analysis and reporting

* Considered an author of this report

5. MILESTONES

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

Milestone:	Planned Date:	Actual Date:
Start of data collection	01 January 2017	04 January 2017
End of data collection	31 March 2017	31 March 2017
Registration in the EU PAS register	Not applicable	14 November 2016
Final report of study results	6 months after the end of data collection (30 September 2017)	July 2017

6. BACKGROUND AND RATIONALE

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

In March 2013, the EMA's PRAC initiated a review of domperidone-containing medicines at the request of the FAMHP, under Article 31 of Directive 2001/83/EC over concerns about cardiac adverse effects of domperidone. This review resulted in changes to the maximum recommended daily dose and for the approved indication. Subsequently, the PRAC recommended that the product label SmPC and Patient Information Leaflet PIL of domperidone-containing medicines be updated to reflect these updates and 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, for the treatment of GERD, for the treatment of diabetic and non-diabetic gastroparesis, and for the treatment of symptoms of postural hypotension in Parkinson's patients.

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

- restriction of the indication to nausea and vomiting;
- recommended limitation of duration for usual use to 7 days;
- reduction of the maximum daily dose to 10 mg TID for adults and adolescents (12 years of age and older and weighing 35 kg or more);

- reduction of the maximum daily dose to 0.25 mg/kg TID for neonates, infants, children (less than 12 years of age), and adolescents weighing less than 35 kg; - measuring devices should be included with liquid formulations to allow accurate dosing by bodyweight;

- 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.

In April 2014, the CMDh endorsed by majority the PRAC recommendation that domperidone-containing medicines be restricted and used only to relieve symptoms of nausea and vomiting and agreed to the above changes to the product information. Within the context of risk minimisation measures, the PRAC requested that domperidone MAHs perform a drug utilisation study to assess the effectiveness of the above-mentioned risk minimisation measures and to monitor the off-label use of the drug. This study is one of two studies designed to answer the PRAC request. The present study aims to describe prescriber understanding, knowledge and awareness of the new safety information on domperidone, whilst a separate retrospective database study is being conducted to describe prescribing patterns and the extent to which they comply with the label.

Pursuant to this Article 31 procedure, the PRAC considered that a DHPC was needed to raise awareness of the new recommendations in the product information and other risk minimisation measures. The PRAC also recommended that following the distribution of the DHPC, a DUS should be conducted to assess the effectiveness of risk minimisation measures and to monitor off-label use. In September 2014, the CMDh made a press release stating that MAHs should form a consortium to conduct the study. As such, the study has been conducted as a joint effort of MAHs who agreed to participate in the consortium.

7. RESEARCH QUESTION AND OBJECTIVES

This study was cross-sectional survey of a group of prescribers to assess the awareness of the health care professionals and level of understanding and knowledge detailed in the risk minimisation activities (e.g., DHPC) with respect to the safety and risk management of domperidone. This study is one of two studies recommended. The present study aims to describe prescriber understanding, knowledge and awareness of the new safety information on domperidone, whilst a separate retrospective database study is being conducted to describe prescribing patterns and the extent to which they comply with the label.

The primary objective of the study was to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the change in SmPC and the distribution of DHPC, including:

- indications for domperidone prescribing;
- length of treatment;

- maximum daily dose;
- concomitant use of domperidone and other drugs known to prolong QT-interval or potent CYP3A4 inhibitors;
- contraindicated conditions; and
- treated population characteristics.

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 multi-national, non-interventional cross-sectional study. A physician survey was developed and approved to be administered to a group of prescribers of domperidone to assess the effectiveness of the risk minimisation measures, and specifically to assess the awareness and level of understanding and knowledge regarding the new safety information for domperidone following the change in SmPC and the distribution of DHPC. Data for the survey was collected electronically via the internet.

A survey was designed to establish whether the intervention, which occurred in the past, has been effective and that physicians have adequately understood the new safety information for domperidone to develop corrective actions, if necessary. The survey obtained information on the knowledge regarding the indication for which the drug is being prescribed, the duration of the use of domperidone, and its use with concomitant medications. The survey examined whether respondents prescribe domperidone for selected conditions that are not labelled. The study was conducted in 5 European countries: Belgium, France, Germany, Spain and the United Kingdom.

The survey was split into two parts. Part I screened physicians for eligibility to complete Part II. Part I consisted of questions on demographics (speciality, age, sex, country of practice, practice setting) and awareness of the DHPC. Part I also contained the critical variable used for screening into Part II, this being the prescription of domperidone. If physicians were seen to have prescribed domperidone since receiving the DHPC (or within the last 6 months had they not seen the DHPC) they were screened into Part II of the study survey. Part II contained the outcomes of interest.

Several study designs were examined to determine the most adequate methodology to meet the study objective, i.e., measuring the effectiveness of the risk minimisation activities for domperidone. Most of the outcomes of interest for this DUS, including physician understanding and awareness of indication, dose, and duration of use cannot be obtained from healthcare databases. As such a survey was deemed most appropriate to assess meet the main objective of the current study with an additional retrospective database analysis being conducted to determine the prescribing patterns of domperidone. This two-study approach ensures the optimum

methodology is used for the relevant objective. The survey's questions about recent, relatively minor health events ask about those that have occurred in the past 2 weeks due to the limitations of patients' recall for more remote events. It was therefore concluded that measuring the effectiveness of the risk minimisation activities for domperidone can best be assessed by a physician survey.

9.1.2. Changes in Conduct

There were no changes to the conduct of the study.

9.2. Setting

The study population comprised of healthcare practitioners specialising in the following 5 areas of medicine: primary care practice (PCP, general practice and internal medicine), gastroenterology, obstetrics/gynaecology, neurology, and paediatrics. The eligible physicians were further screened through Part I of the study survey to determine their inclusion in the study. The distribution of contacted physicians by speciality was based on the estimated domperidone prescribing patterns in each country.

Physician inclusion in the study was based on their prescribing or plans of prescribing domperidone. The population of prescribers was chosen for their potential to be the most representative specialists of the domperidone prescribers and to prescribe domperidone more frequently for the approved label or off-label indications. Domperidone off-label prescribing was expected for the following indications: treatment of GERD, dyspepsia, irritable bowel syndrome (IBS), gastroparesis, symptoms of postural hypotension in patients with Parkinson's disease and increase of breast milk production in lactating mothers (PRAC assessment report, 2014).

The sampling of prescribers in the participating countries was identified from a market research database of Health Care Providers (HCPs). Physicians from the database were invited to participate according to their speciality. An email to the identified prescribers was sent twice a week to inform them about the study and to provide them with the link to the online survey. In addition, prescribers in Belgium were recruited using telephone calls.

To provide an empirical estimate of the enrolled sample representativeness, a register for all eligible physicians is reported where possible. The register contains information from both participating and non-participating physicians who were identified and include the following information, if available: age, sex, speciality, and clinical practice type, and country. This register provides some insight on participation rates and potential selection bias.

9.3. Variables

Specifically, the physicians were tested on their knowledge of the following clinical parameters of domperidone treatment:

- approved indication of treatment,
- maximum recommended usual duration of use,

- maximum daily dose for adults and adolescents,
- maximum daily dose for children less than 12 years of age,
- contraindication of concomitant medications,
- contraindication of pre-existing conditions,

The primary study endpoint was the physician knowledge and understanding of the new safety information for domperidone, as detailed in the SmPC and DHPC. Evaluations included indications for domperidone prescribing, length of treatment, maximum daily dose, concomitant use of domperidone, contraindicated conditions, and treated population characteristics. An additional variable captured the prescribing behaviour of domperidone for off-label indications.

Exception for Questions 3 and 4 in Part II, adequate knowledge and understanding were defined as a correct answer to the question (dichotomous variable). In addition, Part I of the survey collects prescriber characteristic data including, age, sex, speciality, clinical practice type, and country. Survey questions were mostly closed-ended questions with multiple choice answer options only (to minimise error and interpretability error), and took approximately 10 minutes to complete.

Variables that used in the analyses are listed below.

Variable	Source	Role	Value(s)
Physician speciality	Part 1 Q1	Subgroup identifier	a) Primary Care Provider (general practice or internal medicine) b) Gastroenterologist c) Obstetrician/Gynaecologist d) Neurologist e) Paediatrician f) Other (please specify):
Country of practice	Part 1 Q2	Subgroup identifier	a) France b) Germany c) United Kingdom d) Belgium e) Spain
Primary practice	Part 1 Q3	Subgroup identifier	a) Primary care b) Specialist ward c) Academic institution d) Secondary care e) Outpatient care f) Other (please specify):
Age	Part 1 Q4	Physician characteristic/ Covariate	a) 20-29 b) 30-39 c) 40-49 d) 50-59 e) 60+
Sex	Part 1 Q5	Physician characteristic/ Covariate	a) Male b) Female
Have you received the Direct Healthcare Professional Communication	Part 1 Q6	Screener	a) No b) Yes

Variable	Source	Role	Value(s)
(DHPC) on the use of domperidone dated 2014-2015?			
Have you prescribed domperidone products in the last 6 months?	Part 1 Q7	Screener	a) No b) Yes
Have you prescribed domperidone products since receiving the DHPC?	Part 1 Q8	Screener	a) No b) Yes
Approximately how many prescriptions have you written for domperidone in the last 30 days?	Part 1 Q9	Subgroup identifier	a) 0 prescriptions b) 1-5 prescriptions c) 6-10 prescriptions d) 11-20 prescriptions e) 21 or more prescriptions
What is an approved indication of domperidone?	Part 2 Q1	Evaluator/ single response (Evaluation Q1)	a) Dyspepsia b) Nausea and vomiting c) Reflux esophagitis
What is the maximum recommended usual duration of use?	Part 2 Q2	Evaluator/ single response (Evaluation Q2)	a) 7 days b) 30 days c) No limitation
Do you readily know the dosing recommendations?	Part 2 Q3	Subgroup identifier/ single response	a) Yes b) No
Do you have access to a prescribing guide? (All who do not know the recommendations)	Part 2 Q4	Subgroup identifier/ single response	a) Yes b) No
What is the maximum daily dose for adults and adolescents (12 years of age and older and weighing 35 kg or more)?	Part 2 Q5	Evaluator/ single response (Evaluation Q3)	a) 80 mg per day (20 mg QID) b) 30 mg per day (10 mg TID) c) 10 mg per day (10 mg QD)
What is the maximum daily dose for neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35 kg?	Part 2 Q6	Evaluator/ single response (Evaluation Q4)	a) 0.25 mg/kg up to three times per day b) 0.25 mg/kg three to four times per day c) 0.10 mg/kg up to three times per day
Concomitant use of domperidone with which of the following drugs is contraindicated? Check all boxes that apply.	Part 2 Q7	Evaluator/ multi response (Evaluation Q5)	a) Drugs that shorten the QT interval b) Drugs that prolong the bleeding time c) Drugs that prolong the QT interval d) Drugs that are potent CYP3A4 inhibitors
In which underlying disease(s) is domperidone use contraindicated? Check all boxes that apply.	Part 2 Q8	Evaluator/ multi response (Evaluation Q6)	a) Prolactin-releasing pituitary tumour (prolactinoma) b) Moderate to severe hepatic impairment

Variable	Source	Role	Value(s)
			c) Prolongation of cardiac conduction intervals, particularly QTc d) Cardiac insufficiency e) Significant electrolyte disturbance f) Patients with a history of seizures g) Patients with phaeochromocytoma
In view of the revised label, would you prescribe domperidone for any of the following? Check all boxes that apply.	Part 2 Q9	Evaluator/ multi response (Evaluation Q7)	a) Postural hypotension in patients with Parkinson's disease b) Stimulation of lactation in breastfeeding women c) Gastroparesis d) Treatment of gastro-oesophageal reflux disease (GERD) e) Dyspepsia f) Irritable Bowel Syndrome (IBS) g) Relief of the symptoms of nausea and vomiting

9.3.1. Evaluation of Safety

The study was designed to assess the awareness of the health care professionals and level of understanding and knowledge detailed in the risk minimisation activities (e.g., DHPC) with respect to the safety and risk management of domperidone amongst prescribers. As such an evaluation of safety was not part of the primary objectives of the study.

Adverse Events

As per the study protocol, any AEs identified during the data collection for the study were to be forwarded to the MAH responsible for the product, as well as each AE with an unidentifiable MAH to applicable MAH(s) who have product authorization in the concerned country. These events were to be reported using the National AE/ADR reporting form, to be submitted by fax or e-mail within 24 hours of the receipt.

Concomitant Medications

Data on concomitant therapies were collected, again in a general way and as such no AEs were raised. These are documented in Part II Q7 and Q8 of the survey and are reported in the results.

9.4. Data Sources and Measurement

The survey was conducted using a multiple choice survey via the internet to address the most important safety information in the DHPC and potential off-label use. The survey was translated into the local language in each country and administered to HCPs across Belgium, France, Germany, Spain and the United Kingdom.

Part I of the survey established whether physicians met the criteria for inclusion in the analysis of survey data and Part II contained multiple choice questions to collect information on the awareness of the changes to the SmPC.

The survey was conducted by an independent contract research organisation (CRO), Adelphi Real World. The survey was tested after obtaining responses from approximately 5% of physicians in each country. The purpose of this test was to assess clarity of the questions, comprehension and acceptability of the designed instrument.

9.5. Bias

To avoid potential selection bias, all eligible physicians were offered an opportunity for data collection in the study. As with most surveys, the sampling frame and the recruitment of participants can introduce selection bias and may influence the representativeness of the study population. To minimise such selection bias, the following aspects were considered and addressed in the study, including attempt to use a large sampling frame, considering physician's speciality, country, and other characteristics. An attempt was made to have a heterogeneous sample of physicians with appropriate diversity to allow stratification by key characteristics. Furthermore, the demographic characteristics of responders were compared with those of non-responders where possible (HCPs contacted for the survey but not responding). This register of non-respondent demographics was collected to provide insight on potential selection bias. These data are presented in the results section.

9.6. Study Size

A sample size of approximately 400 respondents per country produces a two-sided 95% confidence interval with a width equal to 9.6% when the expected proportion for each country is 60% (please note Belgium has a lower sample of 280 with an increased width equal to 11.4%). However, the numbers were split across the different disciplines of GPs, Gastroenterologists, Neurologists, Obstetrics/Gynaecologists and Paediatricians. This population was chosen for their potential to prescribe domperidone more frequently for the approved label or off-label indications. The speciality split for each country was as follows:

		Total	PCP	Gastro	Ob/Gyn	Neurol	Paed
Belgium	**Expected**	280	100	40	50	40	50
	Observed	277	100	40	47	40	50
	% achieved	99	100	100	94	100	100
France	**Expected**	400	200	50	50	50	50
	Observed	393	200	50	48	50	45
	% achieved	98	100	100	96	100	90
Germany	**Expected**	400	200	50	50	50	50
	Observed	394	200	50	50	50	44
	% achieved	99	100	100	100	100	88
Spain	**Expected**	400	200	50	50	50	50
	Observed	353	200	50	17	50	36
	% achieved	88	100	100	34	100	72

UK	**Expected**	400	200	50	50	50	50
	Observed	388	200	50	38	50	50
	% achieved	97	100	100	76	100	100
Total	**Expected**	1,880	900	240	250	240	250
	Observed	1805	900	240	200	240	225
	% achieved	96	100	100	80	100	90

Please note that the sample size that could be achieved in Belgium was lower than that for the other countries in the study. For descriptive results, the sample size impacts the precision of point estimates (means, percentages, etc.).

9.7. Statistical Methods

Statistical analyses were performed by or under the authority of the sponsor. Part II, Questions 1, 2, 5, 6, 7, 8, and 9 of the survey were scored as 'Correct' or 'Incorrect'. Each question has been analysed separately for the proportion of HCPs with correct answers.

The primary analysis presents the rate of correct answers per question for all countries pooled together, as per the protocol (Protocol - RRA-17004). An additional analysis includes the rates of correct answers by country. The proportion of physicians who potentially prescribe domperidone for unapproved indications is described as per question 1 and question 9 of Part II.

As per the protocol (Protocol - RRA-17004) point estimate and 95% confidence interval (CI) of percent of HCPs with correct responses to each question are presented. The primary analysis presents the rate of correct answers for all countries pooled together. The secondary analysis presents the rates of correct answers by country.

Where possible, the time in practice of the non-responders was banded to match the time in practice of were asked of responders. The comparisons included describe both groups and performing chi^2 tests (or Fisher's exact tests for the 2x2 cases). A $p<0.05$ indicates a statistical difference between responders and non-responders. Only data where a statistical difference exists between respondents and non-respondents is presented side by side for comparative reasons.

9.7.1. Main Summary Measures

Descriptive statistics were used for evaluation and comparison of prescriber knowledge and awareness as measured by the study survey. The study population was described using the demographic characteristics age, sex, speciality, clinical practice type, and country. Only categorical variables were collected and described using frequencies. This involved reporting the base (n) and percentage (%) for each variable by the total (i.e., all countries combined) and then stratified by the country. Further stratification by frequency of use (Part I, Q9) is reported.

9.7.1.1. Safety Analyses

Adverse Events

All questions were categorical and asked in a general way as such no AEs were raised. No event could be associated to a specific patient. Q1 and Q3 of Part I of the study survey contained open text response options for respondents who selected the 'Other' (please specify)' option. The verbatim responses from these questions were reviewed and found to contain no adverse events.

9.7.2. Main Statistical Methods

9.7.3. Missing Values

All missing data are reported. However, as respondents were forced to answer each question in the survey, missing data only affect the non-respondents. Missing data is reported for cases where as 'data not available' it was not possible to report demographic data for non-respondents.

9.7.4. Amendments to the Statistical Analysis Plan

No deviations from the statistical analysis plan were made.

9.8. Quality Control

Given that all interviews were conducted online, the survey was scripted to ensure that the data delivered be clean and free of errors. This also ensured that no interviewer bias affected the quality of the interviews. In order to determine the eligibility of responding physicians, surveys were considered non-valid if Part I (physician characteristics and screening) was not filled in.

10. RESULTS

The results are presented according to the following 3 physician cohorts:

1. 'Responding physicians' – physicians who completed Part I of the study survey and proceeded to complete Part II.

2. 'Screened out' – physicians who completed Part I of the study survey but were ineligible to proceed to Part II of the study survey. As these physicians had completed Part I the demographic data available is in the same format as that of the participating physicians.

3. 'Non-responding physicians' – physicians who were invited to participate in the survey but did not proceed to Part I of the study survey.

Across all countries the quota was met for the PCP, gastroenterologist and neurologist specialities with a total of 1,380 completed surveys (900 PCPs, 240 gastroenterologists, 240 neurologists) (Table 1). Conversely, the target sample size for this epidemiological study was not met for the obstetrician/gynaecologist and paediatrician specialities with a total of 425 complete surveys (200 obstetricians/gynaecologists, 225 paediatricians) (Table 1). At a total level, this represented 75 less surveys than the quota. More incomplete quotas were observed in Spain where the number of completes for obstetricians/gynaecologists was 33 short and 14 short for paediatricians. However, it was observed that more physicians within these two specialities were screening out after Part I of the study survey than were proceeding to Part II. Across all countries 318 obstetricians/gynaecologists and 270 paediatricians screened out after Part I (Table 1). This indicated that these specialities were less likely to be prescribing domperidone as they were screening out based on the lack of prescribing domperidone since receiving the DHPC (or within the last 6 months had they not received the DHPC). This was observed across all countries. A large number of PCPs also screened out (252 PCPs). This indicated that not all PCPs were regularly prescribing domperidone containing products.

There were 435 physicians who tried to complete the study survey after the quota had been met for their speciality. These physicians were unable to complete the survey (either Part I or Part II) as the quota had been met in their country for their speciality and links were therefore inaccessible. Across all countries 294 PCPs, 50 gastroenterologists and 85 neurologists were unable to complete the survey following completion of the quota. It should be noted it is not possible to distinguish these physicians from the remaining non-responding physicians.

Table 1: Physician Speciality and Country of Practice (All Physician Cohorts)					
	Target	**To Be Achieved**	**Completed full questionnaire**	**Quota Full***	**Screened Out**
Total					
PCP	900	0	900	294	252
Gastroenterologist	240	0	240	50	47
Obstetrician/Gynaecologist	250	50	200	1	318
Neurologist	240	0	240	85	41
Paediatrician	250	25	225	5	270
Total	1880	75	1805	435	928
Belgium					
PCP	100	0	100	118	6
Gastroenterologist	40	0	40	21	2
Obstetrician/Gynaecologist	50	3	47	0	33
Neurologist	40	0	40	11	13
Paediatrician	50	0	50	3	8
Total	280	3	277	153	62
France					
PCP	200	0	200	17	70
Gastroenterologist	50	0	50	12	23
Obstetrician/Gynaecologist	50	2	48	0	63
Neurologist	50	0	50	12	4
Paediatrician	50	5	45	0	73
Total	400	7	393	41	233
Germany					
PCP	200	0	200	58	71
Gastroenterologist	50	0	50	1	4
Obstetrician/Gynaecologist	50	0	50	1	91
Neurologist	50	0	50	23	8
Paediatrician	50	6	44	0	122
Total	400	6	394	83	296
Spain					
PCP	200	0	200	64	49
Gastroenterologist	50	0	50	3	11
Obstetrician/Gynaecologist	50	33	17	0	62
Neurologist	50	0	50	36	8

Table 1: Physician Speciality and Country of Practice (All Physician Cohorts)					
	Target	**To Be Achieved**	**Completed full questionnaire**	**Quota Full***	**Screened Out**
Paediatrician	50	14	36	0	38
Total	400	47	353	103	168
United Kingdom					
PCP	200	0	200	37	56
Gastroenterologist	50	0	50	13	7
Obstetrician/Gynaecologist	50	12	38	0	69
Neurologist	50	0	50	3	8
Paediatrician	50	0	50	2	29
Total	400	12	388	55	169

Source: Part 1 Q1: What is your primary medical speciality?
Part1 Q2: Please indicate the country of practice.
**Quota full refers to number of physicians who tried to complete the survey after the quota for their country had been completed and the link was closed.*

10.1. Responding Physician Results

10.1.1. Demographics

The most common primary practice for all countries was primary care (48%). This was highest in France (54%) and lowest in Belgium (40%) (Table 2). Other common primary practice settings were in secondary care (20% overall) and on specialist wards (12% overall). Country differences were observed with the UK having a higher proportion of responding physicians from secondary care than the other countries (34%) and a lower proportion from specialist wards (3%) (Table 2). A fifth of responding physicians from France and Germany were from academic institutions (20% and 21% respectively), whilst this was only true for 3% of the Spanish respondents. Conversely, Spain had high representation in outpatient care (10%) than the other countries (Table 2). Of the 19 respondents who selected 'other, please specify' responses included 'Public health centres', 'Medical-social institutions for disabled adults', 'rehabilitation centre for children with developmental disabilities', 'doctor's office' and 'private hospital'.

Table 2: Primary Practice						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	1805	277	393	394	353	388
Primary care	865	110	214	190	162	189
	48%	40%	54%	48%	46%	49%
Secondary care	366	50	6	88	89	133
	20%	18%	2%	22%	25%	34%
Academic institution	251	41	79	81	11	39
	14%	15%	20%	21%	3%	10%
Specialist ward	213	52	68	28	55	10
	12%	19%	17%	7%	16%	3%
Outpatient care	91	21	13	7	35	15
	5%	8%	3%	2%	10%	4%
Other (please specify):	19	3	13	-	1	2
	1%	1%	3%	-	<1%	1%

Source: Part 1 Q3: your practice is primarily?

Overall, respondents were evenly split across the preassigned age ranges. Whilst <1% were younger than 30 years, 13% were 30-39, 35% were 40-49, 36% were 50-59 and 16% were 60 years or older. Responding physicians in Belgium were younger than other countries with 59% being below 50 years, whilst those in France and Germany were slightly older with 63% and 59% being older than 50 years respectively (Table 3).

Table 3: Physician Age						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	1805	277	393	394	353	388
20-29	8	2	2	1	3	-
	<1%	1%	1%	<1%	1%	-
30-39	234	63	40	27	59	45
	13%	23%	10%	7%	17%	12%
40-49	624	98	103	133	124	166
	35%	35%	26%	34%	35%	43%
50-59	657	67	164	163	126	137
	36%	24%	42%	41%	36%	35%
60+	282	47	84	70	41	40
	16%	17%	21%	18%	12%	10%

More of the respondents were male (74%) than female (26%). This 3 to 1 ratio was observed across all countries expect in Belgium and Spain where it was closer to 2 to 1 for male to female (Belgium 66% male, 34% female; Spain 69%, 31% female) (Table 4).

Table 4: Physician Sex						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	1805	277	393	394	353	388
Male	1334	183	308	308	244	291
	74%	66%	78%	78%	69%	75%
Female	471	94	85	86	109	97
	26%	34%	22%	22%	31%	25%

Source: Part 1 Q5: your sex is?

10.1.2. Screening Data

A relatively even split was observed between physicians who had received the DHPC and those who had not. This split was not equal across all countries with only 27% of Spanish and 30% of German respondents saying they had received the DHPC (Table 5). The highest proportion of respondents stating that they had received the DHPC was in the UK (65%). Whilst similar proportions were seen when split by speciality, a lower proportion of obstetricians/gynaecologists and paediatricians reported receiving the DHPC than other specialities (39% and 42% respectively) (Table 5).

Table 5: Has Physician Received DHPC?						
By Country						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	1805	277	393	394	353	388
Yes	846	162	219	118	95	252
	47%	58%	56%	30%	27%	65%
No	959	115	174	276	258	136
	53%	42%	44%	70%	73%	35%
By speciality						
	Total	**PCP**	**Gastro**	**Obs/Gyn**	**Neuro**	**Paed**
Base	1805	900	240	200	240	225
Yes	846	409	130	78	135	94
	47%	45%	54%	39%	56%	42%
No	959	491	110	122	105	131
	53%	55%	46%	61%	44%	58%

Source: Part 1 Q6: Have you received the Dear Healthcare Professional Communication (DHPC) on the use of domperidone dated 2014-2015?

Of the physicians who screened into Part II of the study survey, 53% stated they hadn't received the DHPC but had prescribed domperidone in the past 6 months whilst 47% stated they had received the DHPC and had prescribed domperidone since (Table 6). There were differences observed between countries with only 27% and 30% of domperidone prescribers in Spain and Germany having received the DHPC respectively compared to over 50% in the other countries. Physicians were screened into Part II of the study survey based on having responded 'yes' to

either question 7 or 8 in Part I of the study survey (answers to both questions presented in Table 6). For a breakdown of physicians' demographic data regarding screened out respondents, please see Section 10.1.2.

Table 6: Has Physician Prescribed Domperidone Products?

	Total	Belgium	France	Germany	Spain	United Kingdom
Base	1805	277	393	394	353	388
Not received DHPC, but prescribed domperidone in past 6 months	959	115	174	276	258	136
	53%	42%	44%	70%	73%	35%
Received DHPC, and prescribed domperidone since	846	162	219	118	95	252
	47%	58%	56%	30%	27%	65%

Source: Part 1 Q7: have you prescribed domperidone products in the last 6 months?
Part 1 Q8: have you prescribed domperidone products since receiving the DHPC?

Approximately half of physicians (56%) prescribed domperidone 1-5 times in the last 30 days. High usage of domperidone (prescribed greater than 10 times in last 30 days) was not overly common across all countries (14%) but was slightly higher in Belgium (20%) and Spain (20%) (Table 7). Most responding physicians stated they made between 1-5 prescriptions (56%) or 6-10 prescriptions (24%) in the past 30 days (Table 7). This observation was common across all countries but domperidone prescribers in the UK were observed to be issuing between 1-5 prescriptions (71%).

Table 7: Approximate Number of Domperidone Prescriptions in the Last 30 Days

	Total	Belgium	France	Germany	Spain	United Kingdom
Base	1805	277	393	394	353	388
0 prescriptions	99	16	22	13	8	40
	5%	6%	6%	3%	2%	10%
1-5 prescriptions	1014	139	209	222	169	275
	56%	50%	53%	56%	48%	71%
6-10 prescriptions	430	68	94	114	103	51
	24%	25%	24%	29%	29%	13%
11-20 prescriptions	169	33	47	31	44	14
	9%	12%	12%	8%	12%	4%
21 or more prescriptions	93	21	21	14	29	8
	5%	8%	5%	4%	8%	2%

Source: Part 1 Q9: Approximately how many prescriptions have you written for domperidone in the last 30 days?

10.1.3. Main Results – Evaluation Questions

Most respondents correctly answered the questions 'What is an approved indication of domperidone?' with 80% knowing its indication for nausea and vomiting. The proportion of correct answers were highest in Belgium (85%) and lowest in Spain (77%) (Table 8).

Table 8: Evaluation Q1 - What is an Approved Indication of Domperidone?

	Total	Belgium	France	Germany	Spain	United Kingdom
Base	1805	277	393	394	353	388
Nausea and vomiting	1449	236	313	318	272	310
	80%	85%	80%	81%	77%	80%
Reflux esophagitis	185	15	53	22	28	67
	10%	5%	13%	6%	8%	17%
Dyspepsia	171	26	27	54	53	11
	9%	9%	7%	14%	15%	3%
Correct†	1449	236	313	318	272	310
	80%	85%	80%	81%	77%	80%
Incorrect	356	41	80	76	81	78
	20%	15%	20%	20%	23%	20%

Source: Part 2 Q1: What is an approved indication of domperidone?
†Correct answer = 'Nausea and vomiting'

Most physicians responded to the evaluation question 'What is the maximum recommended usual duration of use' correctly with 70% stating 7-days; thus 30% responded incorrectly (Table 9). Responses varied across countries with Belgium and France having a lower proportion of incorrect responses (16% and 18%, respectively) compared to Germany (37%), Spain (39%) and the UK (36%) (Table 9).

Table 9: Evaluation Q2 - What is the Maximum Recommended Usual Duration of Use?

	Total	Belgium	France	Germany	Spain	United Kingdom
Base	1805	277	393	394	353	388
7 days	1266	232	322	247	216	249
	70%	84%	82%	63%	61%	64%
30 days	296	16	42	82	82	74
	16%	6%	11%	21%	23%	19%
No limitation	243	29	29	65	55	65
	13%	10%	7%	16%	16%	17%
Correct†	1266	232	322	247	216	249
	70%	84%	82%	63%	61%	64%
Incorrect	539	45	71	147	137	139
	30%	16%	18%	37%	39%	36%

Source: Part 2 Q2: What is the maximum recommended usual duration of use?
†Correct answer = '7 days'

The majority of physicians stated they knew the dosing recommendations for domperidone (79%) nevertheless, this varied across countries. In Spain, a greater proportion of respondents stated they knew the dosing requirements (93%) which contrasted to Germany which had the lowers proportion (64%) (Table 10).

Of the responding physicians who didn't know the dosing requirements, 86% were able to access a prescribing guide. A total of 55 responding physicians (3%) in the survey didn't know the dosing requirements and were unable to access a prescribing guide at the time of completing the survey (Table 10).

Table 10: Do Physicians Know Dosing Recommendations or Have Access to Prescribing Guide?

	Total	Belgium	France	Germany	Spain	United Kingdom
Do you readily know the dosing recommendations?						
Base	1805	277	393	394	353	388
Yes	1418	223	339	252	330	274
	79%	81%	86%	64%	93%	71%
No	387	54	54	142	23	114
	21%	19%	14%	36%	7%	29%
If the answer to Q3 is no to dosing recommendations, do you have access to a prescribing guide?						
Base	387	54	54	142	23	114
Yes	332	40	47	120	22	103
	86%	74%	87%	85%	96%	90%
No	55	14	7	22	1	11
	14%	26%	13%	15%	4%	10%

Source: Part 2 Q3: Do you readily know the dosing recommendations?
Part 2 Q4: If the answer to question 3 is no, do you have access to a prescribing guide?

Most responding physicians correctly chose the maximum daily dose for adults and adolescents (12 years of age or older and weighing 35 kg or more) as 84% stated 30 mg per day (10 mg TID). There were slightly higher proportions of correct responses in Belgium and France (89% in each) compared to Germany (79%) (Table 11). A similar observation was seen when looking at responding physicians who state they readily knew the daily dose or alternatively, had access to a prescribing guide.

Of the responding physicians who stated that they did not have access to a prescribing guide (55 respondents) 69% correctly identified the maximum dose and 31% could not identify the correct dosing (Table 11).

Table 11: Evaluation Q3 – Maximum Daily Dose for Adults and Adolescents (12 years of age and older and weighing 35 kg or more)

	Total	Belgium	France	Germany	Spain	United Kingdom
For all physicians						
Base	1805	277	393	394	353	388
30 mg per day (10 mg	1511	247	348	310	290	316

Table 11: Evaluation Q3 – Maximum Daily Dose for Adults and Adolescents (12 years of age and older and weighing 35 kg or more)						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
TID)	84%	89%	89%	79%	82%	81%
80 mg per day (20 mg QID)	207	24	28	62	53	40
	11%	9%	7%	16%	15%	10%
10 mg per day (10 mg QD)	87	6	17	22	10	32
	5%	2%	4%	6%	3%	8%
Correct†	1511	247	348	310	290	316
	84%	89%	89%	79%	82%	81%
Incorrect	294	30	45	84	63	72
	16%	11%	11%	21%	18%	19%
For physicians who answered 'yes' at Q3 or Q4						
Base	1750	263	386	372	352	377
30 mg per day (10 mg TID)	1473	235	342	296	289	311
	84%	89%	89%	80%	82%	82%
80 mg per day (20 mg QID)	200	23	27	59	53	38
	11%	9%	7%	16%	15%	10%
10 mg per day (10 mg QD)	77	5	17	17	10	28
	4%	2%	4%	5%	3%	7%
Correct†	1473	235	342	296	289	311
	84%	89%	89%	80%	82%	82%
Incorrect	277	28	44	76	63	66
	15%	11%	11%	21%	18%	17%
For physicians who answered 'no' at Q4 – has no access to a prescribing guide						
Base	55	14	7	22	1	11
30 mg per day (10 mg TID)	38	12	6	14	1	5
	69%	86%	86%	64%	100%	45%
80 mg per day (20 mg QID)	7	1	1	3	-	2
	13%	7%	14%	14%	-	18%
10 mg per day (10 mg QD)	10	1	-	5	-	4
	18%	7%	-	23%	-	36%
Correct†	38	12	6	14	1	5
	69%	86%	86%	64%	100%	45%
Incorrect	17	2	1	8	-	6
	31%	14%	14%	36%	-	55%

Source: Part 2 Q5: What is the maximum daily dose for adults and adolescents (12 years of age and older and weighing 35 kg or more)?
†Correct answer = '30 mg per day (10 mg TID)'

Sixty three percent (63%) of the physicians selected an incorrect answer for the maximum daily dose for neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35 kg (Table 12). This was higher in Germany (74%) and France (69%) and lower in the UK

(54%). A similar observation was seen when looking at responding physicians who state they readily knew the daily dose or alternatively, had access to a prescribing guide. It is of note that 50% of responding physicians chose a dose lower than the recommended dose. Only 13% of responding physicians chose the dose that was higher than the daily recommended dose (Table 12)

The proportion of physicians who gave an incorrect response was higher amongst those who had previously stated they didn't have access to a prescribing guide (78%) (Table 12). In general, paediatricians were more likely to select the correct answer compared to the responding physician population combined (49% correct vs 37% correct respectively) and this pattern was observed across all countries (Table 12).

Table 12: Evaluation Q4 - What is the Maximum Daily Dose for Neonates, Infants, Children (less than 12 years of age) and Adolescents Weighing Less Than 35 kg?

	Total	Belgium	France	Germany	Spain	United Kingdom
For all physicians						
Base	1805	277	393	394	353	388
0.25 mg/kg up to three times per day	664	117	120	102	147	178
	37%	42%	31%	26%	42%	46%
0.10 mg/kg up to three times per day	901	124	218	248	152	159
	50%	45%	55%	63%	43%	41%
0.25 mg/kg three to four times per day	240	36	55	44	54	51
	13%	13%	14%	11%	15%	13%
Correct†	664	117	120	102	147	178
	37%	42%	31%	26%	42%	46%
Incorrect	1141	160	273	292	206	210
	63%	58%	69%	74%	58%	54%
For physician who answered 'yes' at Q3 or Q4						
Base	1750	263	386	372	352	377
0.25 mg/kg up to three times per day	652	115	120	98	146	173
	37%	44%	31%	26%	42%	46%
0.10 mg/kg up to three times per day	866	114	213	232	152	155
	50%	43%	55%	62%	43%	41%
0.25 mg/kg three to four times per day	232	34	53	42	54	49
	13%	13%	14%	11%	15%	13%
Correct†	652	115	120	98	146	173
	37%	44%	31%	26%	42%	46%
Incorrect	1098	148	266	274	206	204
	63%	56%	69%	74%	59%	54%
For physicians who answer 'no' at Q3 or Q4– doesn't know the dosing recommendations or has no access to a prescribing guide						
Base	55	14	7	22	1	11
0.25 mg/kg up to three times per day	12	2	-	4	1	5
	22%	14%	-	18%	100%	45%

Table 12: Evaluation Q4 - What is the Maximum Daily Dose for Neonates, Infants, Children (less than 12 years of age) and Adolescents Weighing Less Than 35 kg?						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
0.10 mg/kg up to three times per day	35	10	5	16	-	4
	64%	71%	71%	73%	-	36%
0.25 mg/kg three to four times per day	8	2	2	2	-	2
	15%	14%	29%	9%	-	18%
Correct†	12	2	-	4	1	5
	22%	14%	-	18%	100%	45%
Incorrect	43	12	7	18	-	6
	78%	86%	100%	82%	-	55%
For paediatricians						
Base	225	50	45	44	36	50
0.25 mg/kg up to three times per day	110	24	15	18	24	29
	49%	48%	33%	41%	67%	58%
0.10 mg/kg up to three times per day	54	13	11	3	7	20
	24%	26%	24%	7%	19%	40%
0.25 mg/kg three to four times per day	61	13	19	23	5	1
	27%	26%	42%	52%	14%	2%
Correct†	110	24	15	18	24	29
	49%	48%	33%	41%	67%	58%
Incorrect	115	26	30	26	12	21
	51%	52%	66%	59%	33%	42%

Source: Part 2 Q6: What is the maximum daily dose for neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35 kg?
†Correct answer = '0.25 mg/kg up to three times per day

There were two correct answers to the evaluation question 5 'Concomitant use of domperidone with which of the following drugs is contraindicated?'. Overall 27% of the responding physicians identified both correct answers: 'Drugs that prolong the QT interval' and 'Drugs that are potent CYP3A4 inhibitors' as the correct answers, without selecting additional incorrect answers (Table 13).

A much higher proportion of responding physicians identified 1 of the 2 correct answers without selecting an additional incorrect answer (90%). Overall, 87% of responding physicians correctly identified 'Drugs that prolong the QT interval' as a correct answer, whereas 37% did so with 'Drugs that are potent CYP3A4 inhibitors' (Table 13).

Only 6% of responding physicians were unable to provide a correct answer. The pattern of responses was similar across countries.

Table 13: Evaluation Q5 - Concomitant Use Which is Contraindicated for Domperidone						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	1805	277	393	394	353	388
Drugs that prolong the QT interval	1569	254	371	325	262	357
	87%	92%	94%	82%	74%	92%
Drugs that are potent CYP3A4 inhibitors	669	69	148	160	135	157
	37%	25%	38%	41%	38%	40%
Drugs that shorten the QT interval	170	15	39	28	45	43
	9%	5%	10%	7%	13%	11%
Drugs that prolong the bleeding time	126	10	33	30	28	25
	7%	4%	8%	8%	8%	6%
All correct, none incorrect†	465	55	120	105	59	126
	26%	20%	31%	27%	17%	32%
At least 1 correct, none incorrect	1070	197	209	235	228	201
	59%	71%	53%	60%	65%	52%
At least 1 correct, some incorrect	163	13	49	29	33	39
	9%	5%	12%	7%	9%	10%
Incorrect, none correct	107	12	15	25	33	22
	6%	4%	4%	6%	9%	6%

Source: Part 2 Q7: Concomitant use of domperidone with which of the following drugs is contraindicated? Check all boxes that apply.
†Correct answer = 'Drugs that prolong the QT interval' AND 'Drugs that are potent CYP3A4 inhibitors'

As with Q5, there were two correct answers in evaluation Q6, regarding contraindications of domperidone. Most responding physicians correctly selected 'Prolongation of cardiac conduction intervals, particularly QTc' (87%), whilst just under half correctly selected 'Moderate to severe hepatic impairment' (48%).

Only 4% of all responding physicians correctly selected 'Moderate to severe hepatic impairment' and 'Prolongation of cardiac conduction intervals, particularly QTc' whilst not selecting any further incorrect answers (Table 14).

Overall, 18% of responding physicians correctly identified at least one correct answer without any further incorrect answers. Despite this, only 7% of responding physicians didn't select a correct answer at all (Table 14). The pattern of responses was similar across all countries.

Table 14: Evaluation Q6 - Contraindications						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	1805	277	393	394	353	388
Prolongation of cardiac conduction intervals, particularly QTc	1578	259	369	315	288	347
	87%	94%	94%	80%	82%	89%
Moderate to severe hepatic impairment	864	96	195	246	151	176
	48%	35%	50%	62%	43%	45%
Prolactin-releasing pituitary tumour (prolactinoma)	891	136	177	205	184	189
	49%	49%	45%	52%	52%	49%
Significant electrolyte disturbance	687	115	152	170	127	123
	38%	42%	39%	43%	36%	32%
Cardiac insufficiency	654	104	138	137	110	165
	36%	38%	35%	35%	31%	43%
Patients with a history of seizures	333	35	92	71	87	48
	18%	13%	23%	18%	25%	12%
Patients with phaeochromocytoma	261	40	68	55	51	47
	14%	14%	17%	14%	14%	12%
All correct, none incorrect†	67	6	18	20	9	14
	4%	2%	5%	5%	3%	4%
At least 1 correct, none incorrect	322	53	52	59	87	71
	18%	19%	13%	15%	25%	18%
At least 1 correct, some incorrect	1282	205	310	278	212	277
	71%	74%	79%	71%	60%	71%
Incorrect, none correct	134	13	13	37	45	26
	7%	5%	3%	9%	13%	7%

Source: Part 2 Q8: In which underlying disease(s) is domperidone use contraindicated? Check all boxes that apply.
†Correct answers – 'Moderate to severe hepatic impairment' AND 'Prolongation of cardiac conduction intervals, particularly QTc'

In the final evaluation question, 83% of responding physicians stated that in view of the revised label they would prescribe domperidone for the approved indication of domperidone, 'Relief of the symptoms of nausea and vomiting'. However, 33% of responding physicians selected the approved indication alone as half of responding physicians selecting additional responses (Table 15). A greater proportion of obstetricians and gynaecologists selected 'stimulation of lactation in breastfeeding women' than the population as a whole, and this was observed across all countries. Additionally, a greater proportion of neurologists selected 'postural hypotension in patients with Parkinson's disease' than the population as a whole (Table 15).

Table 15: Evaluation Q7 - Indications for Domperidone Since Revised Label						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	1805	277	393	394	353	388
Relief of the symptoms of nausea and vomiting	1500	227	329	323	309	312
	83%	82%	84%	82%	88%	80%
Dyspepsia	643	104	119	166	182	72
	36%	38%	30%	42%	52%	19%
Gastroparesis	627	135	87	150	117	138
	35%	49%	22%	38%	33%	36%
Treatment of gastro-oesophageal reflux disease (GERD)	587	77	114	110	142	144
	33%	28%	29%	28%	40%	37%
Irritable Bowel Syndrome (IBS)	187	5	16	84	52	30
	10%	2%	4%	21%	15%	8%
Stimulation of lactation in breastfeeding women	125	31	15	22	14	43
	7%	11%	4%	6%	4%	11%
Postural hypotension in patients with Parkinson's disease	106	17	24	20	21	24
	6%	6%	6%	5%	6%	6%
Correct, none incorrect†	589	79	163	116	108	123
	33%	29%	41%	29%	31%	32%
Correct, some incorrect	911	148	166	207	201	189
	50%	53%	42%	53%	57%	49%
Incorrect	305	50	64	71	44	76
	17%	18%	16%	18%	12%	20%
Base	200	47	48	50	17	38
Stimulation of lactation in breastfeeding women (obs/gyns only)	27	8	2	8	2	7
	14%	17%	4%	16%	12%	18%
Base	240	40	50	50	50	50
Postural hypotension in patients with Parkinson's disease (Neurologists only)	66	12	14	13	14	13
	28%	30%	28%	26%	28%	26%

Source: Part 2 Q9: In view of the revised label, would you prescribe domperidone for any of the following? Check all boxes that apply.
†Correct answer – 'Relief of the symptoms of nausea and vomiting'

10.1.4. Summary of Evaluation Questions

Table 16presents a summary of correct responses for each evaluation question alongside the confidence intervals. These intervals provide clarity on the reliability of the data collected. It should be noted that correct responses for multiple choice questions (i.e., evaluation questions 5, 6 and 7) are only correct if all correct responses are chosen and no incorrect options are chosen. Further granularity of the proportion of correct responses selected regardless of other options is present in section 10.1.3.

Table 16: Summary of evaluation questions

		Total	Belgium	France	Germany	Spain	United Kingdom
1	Correct (%)	80.3%	85.2%	79.6%	80.7%	77.1%	79.9%
	Lower CI	78.4%	80.5%	75.3%	76.5%	72.4%	75.6%
	Upper CI	82.1%	88.9%	83.3%	84.3%	81.2%	83.6%
	Range	3.7%	8.4%	8.0%	7.8%	8.7%	8.0%
2	Correct (%)	70.1%	83.8%	81.9%	62.7%	61.2%	64.2%
	Lower CI	67.9%	79.0%	77.8%	57.8%	56.0%	59.3%
	Upper CI	72.2%	87.7%	85.4%	67.3%	66.1%	68.8%
	Range	4.2%	8.7%	7.6%	9.5%	10.1%	9.5%
3	Correct (%)	83.7%	89.2%	88.5%	78.7%	82.2%	81.4%
	Lower CI	81.9%	85.0%	85.0%	74.4%	77.9%	77.2%
	Upper CI	85.3%	92.3%	91.3%	82.5%	85.8%	85.0%
	Range	3.4%	7.3%	6.3%	8.1%	8.0%	7.7%
4	Correct (%)	36.8%	42.2%	30.5%	25.9%	41.6%	45.9%
	Lower CI	34.6%	36.5%	26.2%	21.8%	36.6%	41.0%
	Upper CI	39.1%	48.1%	35.2%	30.4%	46.8%	50.9%
	Range	4.4%	11.6%	9.1%	8.6%	10.2%	9.9%
5	Correct (%)	25.8%	19.9%	30.5%	26.6%	16.7%	31.6%
	Lower CI	23.8%	15.6%	26.2%	22.5%	13.2%	27.2%
	Upper CI	27.9%	25.0%	35.2%	31.2%	20.9%	36.4%
	Range	4.0%	9.4%	9.1%	8.7%	7.8%	9.2%
6	Correct (%)	3.7%	2.2%	4.6%	5.1%	2.5%	3.6%
	Lower CI	2.9%	1.0%	2.9%	3.3%	1.3%	2.2%
	Upper CI	4.7%	4.7%	7.1%	7.7%	4.7%	6.0%
	Range	1.8%	3.7%	4.2%	4.4%	3.4%	3.8%
7	Correct (%)	32.6%	28.5%	41.5%	29.4%	30.6%	31.7%
	Lower CI	30.5%	23.5%	36.7%	25.1%	26.0%	27.3%
	Upper CI	34.8%	34.1%	46.4%	34.1%	35.6%	36.5%
	Range	4.3%	10.6%	9.7%	9.0%	9.6%	9.2%

10.2. Screened Out Respondents – Responses from Part I of Study Survey

10.2.1. Demographics

Across all countries 318 obstetricians/gynaecologists and 270 paediatricians screened out following completion of Part I of the study survey (34% were obstetricians/gynaecologists and 29% paediatricians respectively) (Table 17). This suggests that these specialities were low prescribers of domperidone. This pattern was observed across all countries. Additionally, 252 PCPs screened out, though this was to be expected given the large universe size of this physician speciality.

Table 17: Physician Speciality (screened out)

	Total	Belgium	France	Germany	Spain	United Kingdom
Base	928	62	233	296	168	169
Obstetrician/Gynaecologist	318	33	63	91	62	69
	34%	53%	27%	31%	37%	41%
Paediatrician	270	8	73	122	38	29
	29%	13%	31%	41%	23%	17%
PCP	252	6	70	71	49	56
	27%	10%	30%	24%	29%	33%
Gastroenterologist	47	2	23	4	11	7
	5%	3%	10%	1%	7%	4%
Neurologist	41	13	4	8	8	8
	4%	21%	2%	3%	5%	5%

Source: Part 1 Q1: What is your primary medical speciality?
Part1 Q2: Please indicate the country of practice.

Approximately a third of screened out respondents (32%) practiced in the primary care setting (lower in Belgium and higher in France and Germany; 19%, 42% and 41% respectively). The next most common practice setting was secondary care (27% across all countries; but this was <1% in France and 53% in the UK) (Table 18). In contract to the other countries, screened out physicians in Belgium were more likely to work in specialist wards (31%) or academic institutions (24%) as their primary setting (Table 18). Compared to the responding physicians, screened out respondents were slightly more likely to be working in secondary care instead of primary care as their primary practice. (Table 18and Table 2)

Table 18: Primary Practice (screened out)						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	928	62	233	296	168	169
Primary care	328	12	97	120	45	54
	35%	19%	42%	41%	27%	32%
Secondary care	251	15	1	92	54	89
	27%	24%	*	31%	32%	53%
Academic institution	138	15	57	47	4	15
	15%	24%	24%	16%	2%	9%
Specialist ward	137	19	57	16	38	7
	15%	31%	24%	5%	23%	4%
Outpatient care	54	-	15	19	17	3
	6%	-	6%	6%	10%	2%
Other (please specify):	20	1	6	2	10	1
	2%	2%	3%	1%	6%	1%

Source: Part 1 Q3: your practice is primarily?

Screened out respondents were slightly older than responding physicians, with 19% aged 60+ compared to responding physicians (16%) and 41% aged 50-59 compared to responding physicians (36%) (Table 19 and Table 3).

Table 19: Physician Age (screened out)						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	928	62	233	296	168	169
20-29	5	1	-	1	2	1
	1%	2%	-	*	1%	1%
30-39	84	13	20	19	23	9
	9%	21%	9%	6%	14%	5%
40-49	285	16	67	80	53	69
	31%	26%	29%	27%	32%	41%
50-59	376	24	85	129	71	67
	41%	39%	36%	44%	42%	40%
60+	178	8	61	67	19	23
	19%	13%	26%	23%	11%	14%

Source: Part 1 Q4: Your age (in years) is

Sixty five percent (65%) of screened out respondents were male (65%) (Table 20). The responding physicians were comparable in gender split when compared to the screened out physicians but a difference was observed in Belgium (Male; 45% screened out respondents, 66% responding physicians) (Table 20 and Table 4).

Table 20: Physician Sex (screened out)						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	928	62	233	296	168	169
Male	601	28	147	214	106	106
	65%	45%	63%	72%	63%	63%
Female	327	34	86	82	62	63
	35%	55%	37%	28%	37%	37%

Source: Part 1 Q5: your sex is?

10.2.2. Screening Data

The majority of screened out respondents indicated that they had not received the DHPC (70%) compared to approximately half of the responding physicians (53%) (Table 21 and Table 5).

Table 21: Has Physician Received DHPC?						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	928	62	233	296	168	169
Yes	279	25	112	31	36	75
	30%	40%	48%	10%	21%	44%
No	649	37	121	265	132	94
	70%	60%	52%	90%	79%	56%

Source: Part 1 Q6: Have you received the Dear Healthcare Professional Communication (DHPC) on the use of domperidone dated 2014-2015?

Respondents were screened out on Q7 and Q8. Q7 asked those who had not reived the DHPC if they had prescribed domperidone in the past 6 months whilst Q8 asked those who had reived the DHPC in they had prescribed domperidone since. To be eligible for completion of Part I of the study survey they had to respond yes to either Q7 or Q8. Of the 928 physicians who screened out 649 (70%) had not received the DHPC and screened out because they not prescribed domperidone in the last 6 months, whilst 279 (30%) had received the DHPC but screened out as they hadn't prescribed domperidone since. The 279 (30%) who answered 'no' to Q8 were eligible to answer Q9, regarding the number of domperidone prescriptions they had made in the last 30 days, as it was possible they had prescribed domperidone in the last 30 days but not since receiving the DHPC.

Physicians who stated they had received the DHPC but had no prescribed domperidone since were asked how many prescriptions they have made in the last 30 days. The majority of these physicians had made 0 prescriptions in the past 30 days (80%) with a small proportion having made 1-5 (14%) (Table 22). It was assumed that these physicians had not prescribed domperidone since receiving the DHPC and as such were not eligible to continue to Part II of the study survey.

Table 22: Approximate Number of Domperidone Prescriptions in Past 30 days (for physicians screened out i.e. have not prescribed domperidone since receiving the DHPC)?						
	Total	**Belgium**	**France**	**Germany**	**Spain**	**United Kingdom**
Base	279	25	112	31	36	75
0 prescriptions	222	22	91	25	22	62
	80%	88%	81%	81%	61%	83%
1-5 prescriptions	40	2	15	3	8	12
	14%	8%	13%	10%	22%	16%
6-10 prescriptions	12	-	6	1	5	-
	4%	-	5%	3%	14%	-
11-20 prescriptions	4	1	-	2	1	-
	1%	4%	-	6%	3%	-
21 or more prescriptions	1	-	-	-	-	1
	*	-	-	-	-	1%

Source: Part 1 Q9: Approximately how many prescriptions have you written for domperidone in the last 30 days?

10.3. Non-Responding Physician – Demographic Data

Demographic data were collected on non-responding physicians using physician profiles where possible. In total a sample of 55,595 physicians were contacted. Data for non-responding physicians were available on physicians speciality (23,428 physicians), main practice setting (1,515 physicians), and gender (12,883 physicians).

Non-responding physicians were primarily PCPs (47%) but this was lower in the UK (24%). There was a relatively even split between the remaining specialities (Gastroenterologists 12%, Obstetricians/Gynaecologists 15%, Neurologists 16%, Paediatricians 18%). The UK had a higher proportion than average non-responding physicians from Obstetricians/Gynaecologists and Neurologists (22% and 21% respectively) (Table 23). There were no differences observed between responding physicians and non-responding physicians. However, it should be noted that the surveyed population was captured using quotas and as such this is a forced sample.

The pattern of physicians' primary setting was similar across all countries and settings between non- and responding physicians in that an 'all office/clinic' setting was most common however, significant differences were observed ($p<0.01$ x^2 of responding physicians vs non-responding physicians). Non-responding physicians were more likely to have their primary setting in an 'all hospital' environment than responding physicians (23% vs 18% respectively,) (Table 23). When analysing at a country level the variation in setting was not observed to be significant in Spain and the UK ($p=0.371$, $p=0.222$ respectively, x^2 of responding physicians vs non-responding physicians). Non-respondents in Belgium were more likely to be 'office/clinic' based than responding physicians whilst this difference was less so in France and Germany.

Data captured on average numbers of years in practice demonstrated there were no significant differences between the non-responders and responders, both at a total level and at the country level. However, it should be noted that data on this was limited for both groups.

The gender split of the non-responders and responders followed a similar trend at the global and country level in that there were more males than females. However, this difference was less pronounced in the non-respondent group which contained a greater proportion of females. This difference was significant for all countries (all p values <0.05) expect Spain (p=0.92) (Table 23).

Table 23: Demographics of Non-respondents

	Physician speciality for non-responders									
	PCP		Gastro		Obs/Gyns		Neuros		Paeds	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Total	23428	42%	6931	12%	8364	15%	8811	16%	8061	14%
Belgium	4786	51%	1140	12%	1180	13%	1138	12%	1064	11%
France	6695	47%	2050	14%	1700	12%	1968	14%	1952	14%
Germany	6407	47%	1305	10%	1563	12%	2189	16%	2025	15%
Spain	2620	41%	620	10%	1327	21%	1028	16%	841	13%
United Kingdom	2920	24%	1816	15%	2594	22%	2488	21%	2179	18%

	Main practice setting – Responding physicians vs non-responding physicians										
		All Hospital		Mainly Hospital		50:50 Hospital:Office		Mainly Office/Clinic		All Office/Clinic		P Value
		n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	
Total	RP	279	18%	227	15%	161	11%	200	13%	647	43%	<0.01
	NRP	1387	23%	753	12%	577	9%	988	16%	2411	39%	
Belgium	RP	17	25%	11	16%	3	4%	6	9%	32	46%	<0.01
	NRP	32	14%	20	9%	17	8%	69	31%	88	39%	
France	RP	89	25%	29	8%	28	8%	32	9%	178	50%	0.021
	NRP	440	32%	123	9%	100	7%	154	11%	564	41%	
Germany	RP	52	14%	52	14%	35	9%	53	14%	190	50%	<0.01
	NRP	464	20%	235	10%	156	7%	366	16%	1054	46%	
Spain	RP	46	14%	56	17%	67	20%	52	15%	115	34%	0.371
	NRP	135	15%	140	16%	179	20%	171	19%	261	29%	
United Kingdom	RP	75	20%	79	21%	28	8%	57	15%	132	36%	0.222
	NRP	316	23%	235	17%	125	9%	228	17%	444	33%	

Table 23: Demographics of Non-respondents

Mean number of years in practice – Responding physicians vs non-responding physicians

	Responders		Non-responders	
	n	*Mean years*	*n*	*Mean years*
Total	1430	25.6	434	26.0
Belgium	69	26.2	15	29.9
France	337	25.0	83	25.5
Germany	361	25.7	153	26.1
Spain	310	26.2	71	25.2
United Kingdom	353	25.5	112	26.2

Physician gender – Responding physicians vs non-responding physicians

		Male		Female		P Value
		n	*%*	*n*	*%*	
Total	RP	933	76	288	24	<0.01
	NRP	9140	71	3743	29	
Belgium	RP	47	94	3	6	0.02
	NRP	499	81	114	19	
France	RP	242	80	59	20	<0.01
	NRP	2422	71	1006	29	
Germany	RP	240	77	70	23	0.03
	NRP	3394	72	1338	28	
Spain	RP	182	69	83	31	0.942
	NRP	1862	69	434	31	
United Kingdom	RP	222	75	73	25	0.01
	NRP	1862	69	851	31	

RP = Responding physician, NRP = Non-responding physician

10.4. Stratification by frequency of prescriptions

Correct responses to each evaluation question were stratified by frequency of use, as obtained from Q9 of Part I of the study survey. Fifty six percent (56%) of physicians reported prescribing domperidone containing products 1-5 times in the past 30 days. The proportion of correct responses did not differ more than 10% between the groups with regards to evaluation questions 1, 2, 3, 4 and 6 but there were some discrepancies observed elsewhere. At evaluation Q5 (concomitant use of domperidone) the proportion of correct answers was higher (40.4%) amongst the lowest prescribers (Table 24). This was also observed at evaluation Q7 with low prescribers correct over 50% of the time and more frequent prescribers not.

Table 24: Summary of Evaluation Questions

			Number of prescriptions in last 30 days				
		Total	**0**	**1-5**	**6-10**	**11-20**	**21 or more**
Base		1805	99	1014	430	169	93
1	Correct (%)	80.3%	77.8%	80.8%	80.7%	79.9%	76.3%
	Lower CI	78.4%	68.7%	78.3%	76.7%	73.2%	66.7%
	Upper CI	82.1%	84.9%	83.1%	84.2%	85.2%	83.8%
	Range	3.7%	16.2%	4.8%	7.4%	12.0%	17.1%
2	Correct (%)	70.1%	75.8%	71.5%	69.3%	65.7%	61.3%
	Lower CI	67.9%	66.5%	68.6%	64.8%	58.3%	51.1%
	Upper CI	72.2%	83.2%	74.2%	73.5%	72.4%	70.6%
	Range	4.2%	16.7%	5.5%	8.7%	14.2%	19.4%
3	Correct (%)	83.7%	84.8%	84.3%	85.3%	78.1%	78.5%
	Lower CI	81.9%	76.4%	81.9%	81.6%	71.3%	69.1%
	Upper CI	85.3%	90.6%	86.4%	88.3%	83.7%	85.6%
	Range	3.4%	14.1%	4.5%	6.7%	12.4%	16.5%
4	Correct (%)	36.8%	38.4%	38.0%	36.5%	33.1%	30.1%
	Lower CI	34.6%	29.4%	35.1%	32.1%	26.5%	21.7%
	Upper CI	39.1%	48.2%	41.0%	41.2%	40.5%	40.1%
	Range	4.4%	18.8%	6.0%	9.1%	14.1%	18.3%
5	Correct (%)	25.8%	40.4%	27.7%	20.2%	21.9%	21.5%
	Lower CI	23.8%	31.3%	25.0%	16.7%	16.3%	14.4%
	Upper CI	27.9%	50.2%	30.5%	24.3%	28.7%	30.9%
	Range	4.0%	19.0%	5.5%	7.6%	12.4%	16.5%
6	Correct (%)	3.7%	6.1%	3.5%	4.0%	3.6%	3.2%
	Lower CI	2.9%	2.8%	2.5%	2.5%	1.7%	1.1%
	Upper CI	4.7%	12.6%	4.8%	6.3%	7.6%	9.0%
	Range	1.8%	9.8%	2.3%	3.8%	5.9%	7.9%
7	Correct (%)	32.6%	55.6%	33.3%	29.1%	26.6%	28.0%
	Lower CI	30.5%	45.8%	30.5%	25.0%	20.5%	19.9%
	Upper CI	34.8%	65.0%	36.3%	33.6%	33.7%	37.9%
	Range	4.3%	19.2%	5.8%	8.6%	13.2%	18.0%

10.5. Adverse Events/Adverse Reactions

No adverse events were reported.

11. DISCUSSION

11.1. Key Results

The study questionnaire was designed to evaluate prescribers' knowledge, understanding and the extent of awareness regarding the new safety information for domperidone. The study results highlighted high levels of understanding with regards to the approved indication, maximum duration of administration and dosing of drugs in adults. There were more moderate levels of correct responses with the remaining questions pertaining to the daily dose in infants and neonates and correct contraindications.

The majority of responding physicians were able to correctly identify the approved indication of domperidone ('Nausea and Vomiting' – 80% correct, Table 8), the maximum recommended duration of usual use ('7 days' – 70% correct, Table 9) and the maximum daily dose for adults ('30 mg per day (10 mg TID)' 84%, Table 11). Across all countries the proportion of physicians with correct answers was similar. Most physicians had access to a prescribing guide when they were unaware of the dosing requirements (86%) and for those who did not, 69% still were able to correctly identify the maximum daily dose for adults. Thus only <1% of the responding physicians did not have access to a prescribing guide and did not know the maximum daily dose for adults.

A moderate to low proportion of responding physicians could identify the correct maximum dose for neonates, infants and adolescents (37%) however; again the gap in knowledge was more marked in responding physicians who were unable to refer to a prescribing guide (22%, Table 12). Though it should be noted that 50% of responding physicians selected the lower dose option, perhaps reflecting a prudent behaviour of physicians. Further to this, 49% of paediatricians correctly identified the maximum daily dose.

A high proportion of responding physicians (87%) could correctly identify 'Drugs that prolong the QT interval' as a contraindication for domperidone with a more moderate proportion (37%) identifying 'Drugs that are potent CYP3A4 inhibitors' as a correct response (Table 13). Responding physicians selected one of the correct answers in 85% of cases but a lower proportion of 26% identified both together.

Again, a high proportion of responding physicians (87%) could correctly identify 'Prolongation of cardiac conduction intervals, particularly QTc' as a disease contraindicated for domperidone, with more moderate levels (48%) correctly identifying 'Moderate to severe hepatic impairment' as a contraindication. Despite these high levels of awareness only 4% identified these two contraindications alone without various other incorrect responses being selected as well (Table 14). Finally, 17% of responding physicians were unable to correctly identify that domperidone should be prescribed for 'Relief of the symptoms of nausea and vomiting' in view of the revised label (Table 15).

The high number of obstetricians/gynaecologists and paediatricians screening out after Part I of the study survey highlighted that these represent low prescribing groups. As a result of the high level of screen outs the quota for both these specialities was not met.

Data collected demonstrated that whilst respondents and non-respondents were still more likely to be male, this was significantly less pronounced in the non-respondents group. Non-responding physicians were most likely to be PCPs and there were no significant differences detected vs responding physicians for time spent practicing medicine. The pattern of primary setting was similar across all countries with an 'all office/clinic' setting being most common in both non- and responding physicians. However, non-responding physicians were significantly more likely to have a primary setting in an 'all hospital' environment than responding physicians.

11.2. Limitations

A research panel was used for identification and recruitment of physicians and therefore the population is more likely to be research active than those not on the panel. However, a panel of physicians allows for wide geographical reach and a wide range of medical practices to be included in a uniform manner. The panel also allows access to a large sample of physicians to provide robust results.

Participation in the study was voluntary. Therefore, there may be differences between respondents and non-respondents. Where possible, the profiles between these two groups were compared on a small number of characteristics (time in practice, gender and practice setting). Whilst the two groups were similar on these characteristics there may be differences in their level of knowledge and awareness.

This survey was designed to assess physician awareness and understanding of the new safety information of domperidone containing products and how well they recalled the information and adhered to it. However, as the delivery of the DHPC informing physicians of the updates to the label was sent in Q3/4 2014 a time lag between deliveries of the DHPC and conducting of the survey in 2016 should be taken into account. Therefore, it is likely that physicians cannot recall all the information provided in the DHPC. Whilst an effort was made to prevent evaluation questions from relying on recall, certain elements of the survey relied on recall which may have resulted in over/under estimation of the endpoint parameters under evaluation (e.g. when reporting how often they prescribed domperidone). Additionally, there were no baseline data available on physician understanding and awareness of the domperidone label prior to the delivery of the DHPC so it is not possible to measure the effectiveness of the DHPC. Previous studies have shown that physician knowledge can often be inconsistent with the product labelling, and greater understanding of these knowledge gaps, and the effectiveness of DHPCs, will be important to ensuring appropriate steps are made [1,2]. The results from this survey more accurately represent physician general knowledge of the domperidone label as opposed to the effectiveness of the DHPC.

Previous studies have highlighted that physician knowledge of potentially clinically significant drug-drug interactions is generally poor [3–5]. Physicians most commonly reported learning about

potential drug-drug interactions from pharmacists. These findings may go some way to explaining the low proportion of physicians who identified the correct drug-drug interactions of domperidone. It has been suggested that automated drug interaction alerts have the potential to dramatically increase physician recognition of drug-drug interactions and in previous studies the idea has been highlighted as a favourable option by physicians [4].

11.3. Interpretation

The data highlight high levels of awareness for the updated label of domperidone containing products. In particular physicians are aware of indications of use, maximum dose duration, maximum dose in adults and concomitant use of domperidone for drugs that are potent QT inhibitors.

However, more moderate to lower awareness was seen with regards to maximum daily dose in children and neonates and contraindications of domperidone.

Physicians demonstrated a high level of awareness of the correct contraindications of domperidone but also selected additional response options. This resulted in a lower overall percentage of 'correct' responses. Additionally, in evaluation Q7 physicians were asked what indications they would prescribe domperidone for. The low percentage of 'correct' responses may not necessarily be due to a lack of knowledge of the approved indication and more an indication of off-label use of domperidone. This is demonstrated by 80% of physicians correctly identifying the approved indication of domperidone in evaluation Q1 however, it should be considered that some physicians may think domperidone is approved for several indications.

In total 53% of the eligible responding physicians claimed to have not received the DHPC. These physicians were still eligible to complete the survey as they had prescribed domperidone containing products in the 6 months prior to the survey. However, it can only be speculated as to why these physicians claimed they had not received the DHPC. It is possible that the DHPC distribution channels did not reach all physicians who completed the survey or that the physician did not recall receiving the DHPC.

Additionally, it was observed that obstetricians/gynaecologists and paediatricians are low prescribers of domperidone. Numerous physicians from these specialities were unable to complete Part II of the study survey due to screening out in Part I of the study.

At the point of submission of this report an additional study is being conducted. This database study will collect data on prescribing patterns and off-label use of domperidone. Prior to the recommendation of any actions, should any be needed, results from both studies should be considered in conjunction.

11.4. Generalizability

The only inclusion criterion for eligibility to participate in the study, was having actively prescribed domperidone in the last 6 months (or since receiving the DHPC). This criterion coupled with the large sample size of this study entail that the results can be applied to a general

domperidone prescriber population. The selection of participating physicians distributed across 5 European countries and various physician specialties was representative for the domperidone-prescribing physicians' groups.

12. CONCLUSION

Responding physicians demonstrated a high level of knowledge on the recommended changes to the domperidone label. Overall, there was a high level of access to prescribing guide; most responding physicians recalled receiving the information and demonstrated working knowledge of the revised/updated product limitations of the indication, dose administration duration, maximum dose and concomitant use of domperidone, though high awareness was observed for concomitant use of domperidone in drugs that prolong the QT interval.

However, the results highlight a limited awareness on:

- the daily doses in infants and neonates and the contraindications of the drug and the reduction in maximum daily dose in children and neonates to 0.25 mg TID as per the recent update in label indication (and so as responding physicians were largely unable to correctly identify this change). Physicians largely selected a lower than recommended dose, perhaps highlighting prudent behaviour in light of limited awareness.

- the right set of contraindications (and so as whilst a majority of responding physicians was able to correctly identify contraindications, they were not able to do so without identifying further incorrect ones).

The findings from this survey will be complemented with those from the database study exploring prescribing patterns and off-label use of domperidone. Possible actions of both studies should be considered in conjunction following completion of the database study in Q4 of 2017.

13. REFERENCES

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4. Glassman, P. A., Simon, B., Belperio, P. & Lanto, A. Improving recognition of drug interactions: benefits and barriers to using automated drug alerts. *Med. Care* **40,** 1161–1171 (2002).
5. Ko, Y. *et al.* Potential determinants of prescribers' drug-drug interaction knowledge. *Res. Soc. Adm. Pharm. RSAP* **4,** 355–366 (2008).

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

9 Documentation of Statistical Methods and Interim Analysis Plans

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

11 Publications Based on the Study

12 Important Publications Referenced in the Report

13 Data Listings

ANNEX 2: ADDITIONAL/SUPPORTING INFORMATION

Annex 2 – NAME AND ADDRESS OF EACH PARTY FOR NOTICE PURPOSES AND REPRESENTATIVE OF EACH PARTY

A detailed list of all EU-MAH submitting this report can be found in Section 4 of this report.

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SIGNATURE OF SPONSOR'S RESPONSIBLE MEDICAL OFFICER

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REPORT CONTRIBUTORS:	Ute Richarz, MD, Peter Hu, PhD

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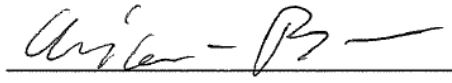
I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE: 

DATE: 19. June 2017