Clinical Drug Investigation (2019) 39:1057–1066
https://doi.org/10.1007/s40261-019-00831-3

ORIGINAL RESEARCH ARTICLE

Awareness of, and Compliance with, Domperidone Revised Labeling After a Risk-Minimization Activity in Europe

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Published online: 19 July 2019

Abstract

Background and Objective Risk-minimization measures (RMM), including label revisions were implemented in Europe for domperidone because of evidence of increased incidence of cardiac arrhythmia and sudden cardiac death. In accordance with the guideline on good pharmacovigilance practices, the European Medicines Agency Pharmacovigilance Risk Assessment Committee requested to conduct two studies to evaluate the effectiveness of these risk minimization measures.

Methods In Belgium, France, Germany, Spain, and the UK, surveys were conducted to assess physicians' knowledge on the updated domperidone labeling information, and a drug-utilization study (DUS) was conducted using healthcare databases to assess domperidone prescribing patterns before and after the RMM. Four DUS sensitivity analyses (scenarios) evaluated uncertainty regarding domperidone treatment duration and indication.

Results Among 1805 physicians participating in the survey, most were aware of the approved indication (nausea and vomiting, 80%), treatment duration (≤ 7 days, 70%), and maximum adult daily dose (10 mg three times daily, 84%). Only 33% selected the on-label indication from a list of indications for which they would prescribe domperidone. Awareness was low for medications contraindicated for concomitant use (26%) and contraindicated conditions (4%). In the DUS, under the optimistic scenario, a large improvement in labeling compliance from pre- to post-implementation period was observed in France (27% vs. 69%), while Belgium, Germany, Spain, and the UK showed small improvements (< 10%). In the other scenarios, there was little to no improvement in compliance with the revised labeling from the pre- to post-implementation periods in most countries.

Conclusions The survey findings documented that most physicians in all five countries were aware of the main aspects of the revised labeling. Results of the DUS were inconclusive regarding the effect of the RMM and compliance with the revised labeling for all countries except France.

1 Introduction

Domperidone, a dopamine (D2) receptor antagonist, is a prokinetic and antiemetic agent first approved in Belgium in March 1978 followed by approval in several European countries and authorized since 2014 for the treatment of acute nausea and vomiting. Although the effect of domperidone on the QT interval is controversial [1–5], several epidemiologic studies found that exposure to domperidone, especially when used at doses above 10 mg three times a day, was associated with an increased risk of serious cardiac arrhythmias and sudden cardiac death [6–11].

In view of these safety concerns, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) initiated a review of domperidone-containing medications in March 2013 and recommended changes to the product labeling [12]. These changes included: (1) restricting the indication to symptoms of nausea and vomiting; (2) limiting duration of use to 7 days; (3) reducing the maximum daily dose for adults and adolescents to 10 mg three times a day (TID) and to 0.25 mg/kg TID for children aged < 12 years and adolescents weighing < 35 kg; (4) contraindicating concomitant use with medications known to

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40261-019-00831-3) contains supplementary material, which is available to authorized users.

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Key Points

In Belgium, France, Germany, Spain, and the UK, a physician survey was conducted to assess the knowledge on the updated domperidone labeling information. In addition, a drug-utilization study (DUS) was conducted using healthcare databases to assess domperidone prescribing patterns before and after the risk management measures (RMM).

The physician survey findings showed that most physicians in all five countries were aware of the main aspects of the revised labeling. The DUS results were inconclusive regarding the effect of the RMM and compliance with the revised labeling for all countries except France.

increase cardiac risks, or increase the domperidone plasma concentration; and (5) contraindicating use in patients with moderate or severe hepatic impairment or certain cardiac conditions [12].

In addition, the PRAC raised concerns about various off-label uses of domperidone in the EU, including stimulation of lactation in breastfeeding women, treatment of symptoms of postural hypotension in Parkinson's patients [12], and treatment of two conditions for which domperidone was previously indicated: gastro-esophageal reflux disease (GERD) and diabetic and non-diabetic gastroparesis. These new recommendations were communicated to physicians by distributing Direct Healthcare Professional Communication (DHCP) letters from 1 April 2014 through 30 September 2014 and via the updated product labeling implemented in 2015.

In accordance with the guideline on good pharmacovigilance practices (GVP) module XVI [13], the PRAC requested that the marketing authorization holders of domperidone conduct two studies to evaluate the effectiveness of these risk minimization activities. In response, a physician survey was conducted in five countries to assess the understanding, knowledge, and awareness of the new labeling information as detailed in the updated summary of product characteristics (SmPC) and DHPC. In addition, a drug utilization study (DUS) was conducted in the same five countries to examine domperidone prescribing patterns before and after the changes to the labeling and the distribution of the DHPC, and to assess the extent of compliance with the new labeling. We report the findings of these two studies.

2 Methods

Both the physician survey and DUS were performed in Belgium, France, Germany, Spain, and the UK. These countries were selected because they offered a range of domperidone usage (from France, with the highest per capita domperidone use in the EU, to Germany, ranked number 12 in the EU for per capita domperidone use), and had robust longitudinal electronic medical record (EMR) databases. The present report focuses on domperidone use in patients ≥ 12 years of age in whom domperidone is widely used. The use of domperidone in children was expected to decrease based on the results of a recent randomized controlled study (ClinTrials.gov NCT02699385) that showed lack of effect at the approved pediatric dose (0.25 mg/kg TID) and led to the removal of domperidone's European indication for use in children.

The physician survey and the DUS were conducted in accordance with all applicable regulatory requirements. Ethics committee approval for conducting the physician survey was obtained in each country, wherever applicable, as per the local requirements. For the DUS, ethics committee approval was required and obtained in the UK and Spain and was not required or obtained in the other countries because it was a retrospective database study from anonymized data. The data for each study were held in a secure study database that complied with the patient privacy regulations of each participating country.

2.1 Physician Survey

This was a cross-sectional study conducted between 4 January 2017 and 31 March 2017 among physicians specialized in primary-care practice (general practice and internal medicine), gastroenterology, pediatrics, obstetrics/gynecology, and neurology. These specialties were chosen due to their potential to prescribe domperidone for approved or off-label indications.

Physicians in each country were sampled from a market research database of healthcare providers and were invited by e-mail to complete the survey on a first-come-first-serve basis until the target sample size was met. Physicians received invitations by e-mail or telephone to participate in an online survey. Up to three follow-ups with non-responders were conducted. Responding physicians were included in the study if they had prescribed domperidone since receiving the DHPC or at least once in the 6 months prior to taking the survey.

The online survey consisted of multiple-choice questions in the local language (Supplementary Fig. 1). Part I of the questionnaire included questions about physician characteristics and determined the eligibility of physicians and Part II included the main questions of the study related to the understanding, knowledge, and awareness of the new labeling information. In part II, data were collected on the knowledge of the indication for domperidone prescribing, length of treatment, maximum daily dose, contraindicated concomitant medications, and contraindicated conditions.

The prescribing behavior for off-label indications was also captured. Questions with more than one correct choice were graded as correct only if all the correct choices and no incorrect choices were selected.

2.2 Drug Utilization Study

This was a retrospective, observational study using a pre-post design for the time between 1 January 2011 and 30 September 2015, which was divided into four time periods: (1) a background period (1 January 2011 through 31 March 2013) to assess use during the pre-implementation period; (2) a 1-year pre-implementation period (1 April 2013 through 31 March 2014); (3) a 6-month implementation period of risk minimization measures (RMM) (1 April 2014 through 30 September 2014) including the DHPC letters and the labeling change; and (4) a 1-year post-implementation period (1 October 2014 through 30 September 2015).

The study cohort was identified from the IQVIA EMR databases for Belgium, France, Germany, and Spain and from the Clinical Practice Research Datalink (CPRD) for the UK. Patients were included if at any time during the study periods they received at least one prescription for domperidone in the outpatient setting that was preceded by membership or registration (or the equivalent of) in the practice and available medical history for ≥ 180 days prior to the domperidone prescription. Patients were followed from the date of the first domperidone prescription until end of study period, transfer out of the practice, or the end of the practice's qualification as up to standard (in CPRD), whichever came first.

The primary study objective was to estimate and compare (before and after the labeling change) the proportion of prescriptions that met a composite endpoint of compliance with the revised labeling regarding: (1) maximum daily dose ≤ 10 mg three times daily, (2) duration of use (≤ 7 days), (3) no concomitant medications that either prolong the QT-interval or are potent CYP3A4 inhibitors, (4) no prescribing to patients with contraindicated conditions (e.g., moderate or severe liver disease, specified cardiac diagnoses), and (5) prescribing for the approved indication (symptoms of nausea and vomiting). The secondary endpoints were the individual components of the composite endpoint for compliance.

2.2.1 Study Measurements

Compliance with the labeling was assessed for each prescription separately. The duration of each prescription was estimated from the days' supply, if available, or calculated as the total quantity prescribed divided by the daily number of pills recommended in the dosing instructions. The indication associated with a prescription was estimated based on the diagnoses recorded shortly before the prescription as follows: nausea and vomiting—on the day of prescription or during the preceding 7 days; GERD, gastric dysmotility, irritable bowel syndrome, suppressed lactation, orthostatic hypotension (with a prior or concurrent diagnosis of Parkinson's disease)—on the day of prescription or in the preceding 2 months. If no diagnoses met these criteria, the indication was considered unknown. If a prescription met the criteria for nausea and vomiting and for another (off-label) indication, the former was selected as the indication. Contraindicated concomitant medications that prolong the QT interval or a potent CYP3A4 inhibitor were defined as those that had ≥ 1 day overlap with the estimated treatment days of domperidone prescription. Contraindicated conditions included diagnosis of hepatic cirrhosis, hepatic failure, or hepatic coma recorded any time up to the date of the prescription; QTc prolongation, ventricular arrhythmia, congestive heart failure during the 6 months before the date of the domperidone prescription, or hypokalemia in the 30 days before the date of the prescription.

Compliance with all labeling requirements was examined with a series of sensitivity analyses performed on the prescription level to address uncertainty related to domperidone treatment duration and indication. Uncertainty regarding the duration of domperidone therapy arose because domperidone is used as needed, so a prescription for more than a 7-day supply could be used for up to 7 or for more than 7 days. There was also uncertainty about the indication because a substantial proportion of prescriptions had no diagnosis that met the above-described criteria for determining the indication for which domperidone was prescribed. To address these uncertainties for prescriptions that met all other labeling requirements but had more than 7 days' supply or unknown indication, the following scenarios were applied:

- Optimistic: unknown indication was assumed to be symptoms of nausea or vomiting (on-label) and duration of use to be ≤ 7 days.
- Intermediate A: unknown indication was assumed to be off-label and duration of use to be ≤ 7 days.
- Intermediate B: unknown indication was assumed to be symptoms of nausea and vomiting (on-label) and duration of use to be the days' supply.
- Pessimistic: unknown indication was assumed to be off-label and duration to be the days' supply.

2.3 Statistical Analysis

Data were analyzed using descriptive statistics for both studies. In the DUS, the composite endpoint was calculated as the number of domperidone prescriptions consistent with the revised labeling as a proportion of domperidone-treated patients and as a proportion of domperidone prescriptions.

Compliance with the composite endpoint and with each of its components was compared between the pre-implementation and post-implementation periods using "risk ratios" (RRs) and 95% confidence intervals (CIs). Missing data were not reported in the DUS and imputations were not undertaken. Analyses of DUS data were done in SAS version 9.4 (SAS Institute, Cary, NC, USA) and analyses of physician survey data were conducted using IBM SPSS Data Collection Survey Reporter.

3 Results

3.1 Physician Survey

Of the total 58,882 physicians who were contacted, 3168 responded. After applying exclusion criteria, removing 928 physicians who were non-prescribers of domperidone-containing products (screened in Part I survey) and 435 physicians who completed the study survey after the quota, 1805 participating physicians completed the survey (Fig. 1). Among participating physicians ($n = 1805$), 900 (50%) were specialized in primary care, 240 (13%) in gastroenterology, and 240 (13%) in neurology, 225 (12%) in pediatrics, and 200 (11%) in obstetrics/gynecology (Supplementary Table 1). The majority of the physicians were male (74%), and 52% were aged ≥ 50 years (Table 1). Of these 1805 physicians, 865 (48%) identified themselves as being in primary care, 366 (20%) in secondary care, 251 (14%) in an academic institution, 213 (12%) in a specialty ward; 91 (5%) in outpatient care and 19 (1%) in "other". Most physicians had written one to five domperidone prescriptions (56%) or six to ten prescriptions (24%) in the 30 days prior taking the survey. A high number of prescriptions (> 10 prescriptions in the last 30 days) was reported among 14% of physicians and no prescriptions in the past 30 days was reported among 5%. A high number of prescriptions (> 10 in the last 30 days) was most common in Belgium (20%) and Spain (20%).

The majority of physicians in all countries correctly responded to questions related to the approved indication for domperidone ("nausea and vomiting": 80%), the maximum recommended duration of use (70%), and the maximum daily dose for adults (84%) (Fig. 2). Most physicians (79%) specified that they were aware of the dosing recommendations for domperidone; however, the response varied across countries. Of those physicians who did not know the

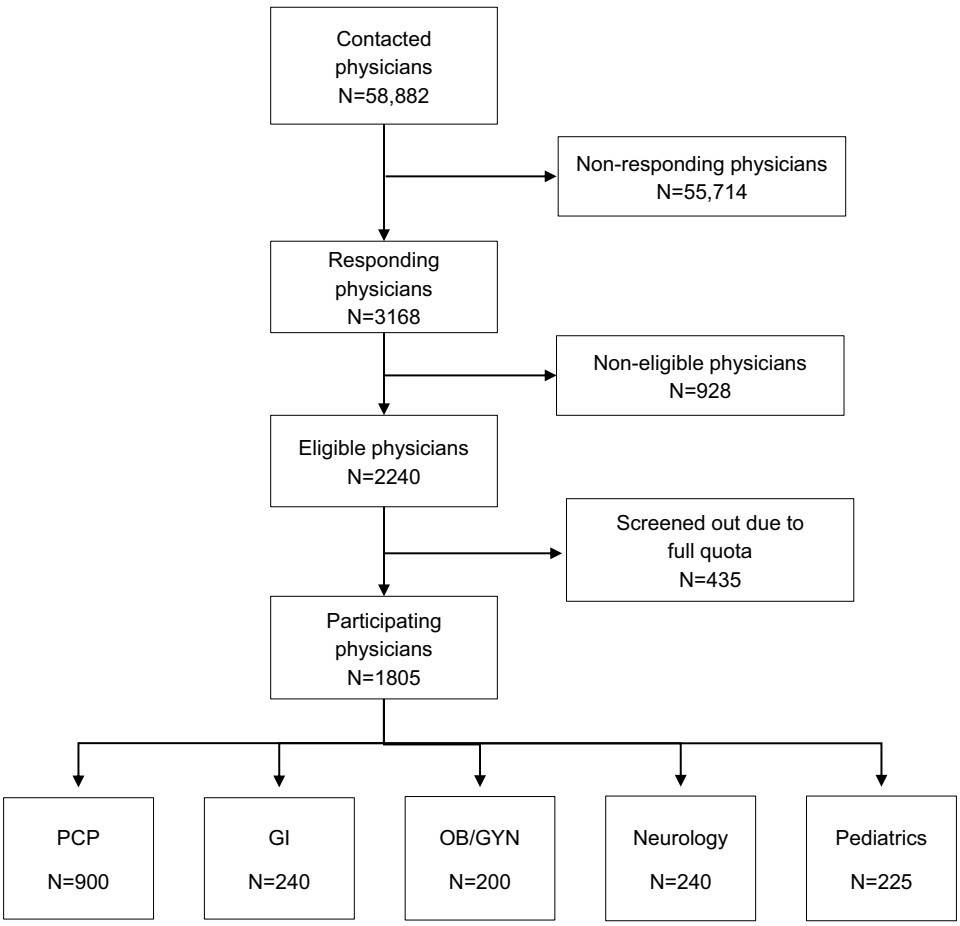

Fig. 1 Physicians' survey—flow chart. Non-responding physicians are who were invited to participate in the survey but did not proceed to Part I of the study survey; 'Responding physicians' are those who completed Part I of the study survey and proceeded to complete Part II; 'Non-eligible physicians' are those who completed Part I of the study survey but were ineligible to proceed to Part II of the study survey. The quota (the planned sample size) was 280 for Belgium, which was a relatively small country, 400 for all the other countries. *PCP* primary-care provider, *GI* gastroenterologist, *OB/GYN* obstetrician/gynecologist

Table 1 Demographics and screening data of the physicians' survey

Characteristics	Total ($n=1805$) *n* (%)	Belgium ($n=277$) *n* (%)	France ($n=393$) *n* (%)	Germany ($n=394$) *n* (%)	Spain ($n=353$) *n* (%)	UK ($n=388$) *n* (%)
Specialty						
Primary-care practice	900 (50)	100 (36)	200 (51)	200 (51)	200 (57)	200 (52)
Gastroenterologist	240 (13)	40 (14)	50 (13)	50 (13)	50 (14)	50 (13)
Obstetrician/gynecologist	200 (11)	47 (17)	48 (12)	50 (13)	17 (5)	38 (10)
Neurologist	240 (13)	40 (14)	50 (13)	50 (13)	50 (14)	50 (13)
Pediatrician	225 (12)	50 (18)	45 (11)	44 (11)	36 (10)	50 (13)
Age (years)						
20–29	8 (0.4)	2 (1)	2 (1)	1 (0.3)	3 (1)	–
30–39	234 (13)	63 (23)	40 (10)	27 (7)	59 (17)	–
40–49	624 (35)	98 (35)	103 (26)	133 (34)	124 (35)	166 (43)
50–59	657 (36)	67 (24)	164 (42)	163 (41)	126 (36)	137 (35)
60+	282 (16)	47 (17)	84 (21)	70 (18)	41 (12)	40 (10)
Sex						
Male	1334 (74)	183 (66)	308 (78)	308 (78)	244 (69)	291 (75)
Female	471 (26)	94 (34)	85 (22)	86 (22)	109 (31)	97 (25)
Has physician received DHPC?						
No	959 (53)	115 (42)	174 (44)	276 (70)	258 (73)	136 (35)
Has physician prescribed domperidone products?						
Received DHPC and prescribed domperidone	846 (47)	162 (58)	219 (56)	118 (30)	95 (27)	252 (65)
Approximate number of domperidone prescriptions in the 30 days prior to taking the survey						
0	99 (5)	16 (6)	22 (6)	13 (3)	8 (2)	40 (10)
1–5	1014 (56)	139 (50)	209 (53)	222 (56)	169 (48)	275 (71)
6–10	430 (24)	68 (25)	94 (24)	114 (29)	103 (29)	51 (13)
11–20	169 (9)	33 (12)	47 (12)	31 (8)	44 (12)	14 (4)
≥21	93 (5)	21 (8)	21 (5)	14 (4)	29 (8)	8 (2)

DHPC Dear Healthcare Professional Communication, *n* number of respondents

dosing recommendations ($n=387$; 21%), 86% were able to access the prescribing guide. The majority of physicians who did not have access to a prescribing guide (69%) were still able to correctly identify the maximum daily dose for adults. Almost half of physicians (47%) correctly answered on the maximum pediatric dose. Pediatricians across all countries were more likely to select the correct pediatric dose compared to the physicians other than pediatricians (49% vs. 35%, respectively; data not shown). Only one-fifth of physicians answered correctly regarding the medications contraindicated for concurrent use (26%), and very few (4%) provided correct response regarding the list of diagnoses that were contraindicated with domperidone use. Most physicians (68%) correctly answered regarding the approved indication for domperidone in a closed-ended question when only one choice could be selected (Q1 in part II). In contrast to the proportion who knew the indication, only 33% indicated they would prescribe domperidone for the approved indication and no other in a question with multiple-response choice.

3.2 Drug Utilization Study

In the optimistic scenario, the proportion of prescriptions meeting all the labeling requirements in the post-intervention period ranged from 50% in Spain to approximately 75% in the UK and Belgium. In France, a large improvement in labeling compliance from the pre-intervention period (27%) to the post-intervention period (69%) was observed with an RR of 2.56 (95% CI 2.52–2.59) (Table 2). Improvement in compliance was small but statistically significant in Belgium, Germany, and the UK (RR 1.06–1.16); a modest decrease in compliance was reported in Spain (RR 0.94; 95% CI 0.92–0.97). In the pessimistic scenario, the proportion of prescriptions meeting all the labeling requirements in the post-intervention period was below 2% except for France, where it was 11%. In intermediate scenario A (optimistic about the duration if days' supply > 7, but pessimistic about indication if unknown), post-intervention compliance was 32% in Belgium, 16% in France, 4% in Germany, and 2% in Spain and the UK. In intermediate scenario B (pessimistic

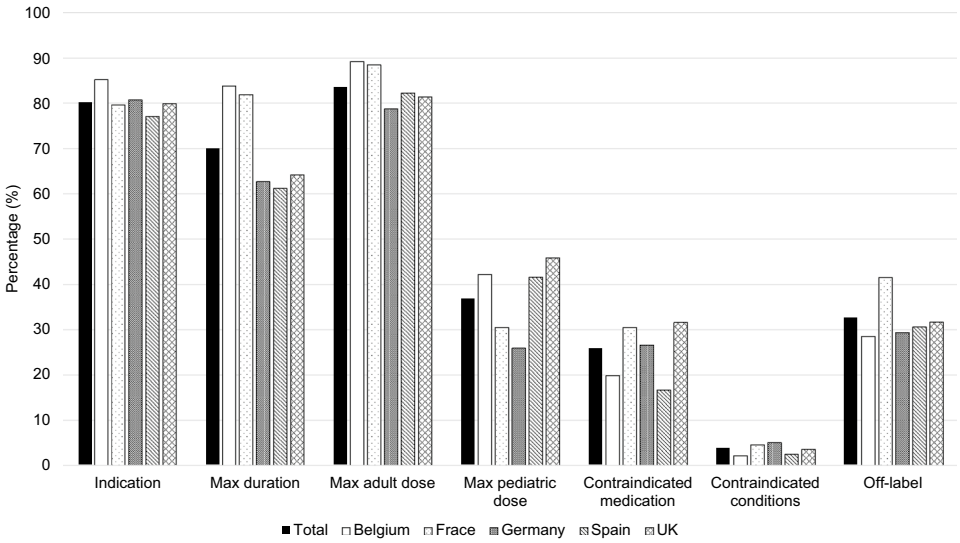

Fig. 2 Proportion of correct responses for each knowledge question by question content and country in the physicians' survey. *Max* maximum

about the duration of use if days' supply > 7, but optimistic about indication if unknown), post-intervention compliance was 46% in France, 16% in Germany, 13% in the UK, 0.1% in Belgium, and 0% in Spain (Table 2).

All countries demonstrated high compliance with the dose limitation, non-use of contraindicated concomitant medications, and non-use in contraindicated conditions (Table 3). There was no change in the compliance in these

Table 2 Number and proportion of prescriptions (adults ≥ 12 years) meeting all requirements of the revised label by scenario (optimistic, intermediate A, intermediate B, or pessimistic) during the pre -and post-implementation periods, drug-utilization study (DUS)

Country	Scenario	Pre-implementation period		Post-implementation period		Post- vs. pre-implementation period
		Prescriptions (*n*)	Label compliant *n* (%)	Prescriptions (*n*)	Label compliant *n* (%)	Risk ratio (95% CI)
Belgium	Optimistic	11,330	8134 (71.8)	16,860	12,896 (76.5)	1.07 (1.05–1.08)
	Intermediate A	11,330	3313 (29.2)	16,860	5430 (32.2)	1.10 (1.06–1.14)
	Intermediate B	11,330	14 (0.1)	16,860	24 (0.1)	1.15 (0.60–2.23)
	Pessimistic	11,330	9 (0.1)	16,860	10 (0.1)	0.75 (0.30–1.84)
France	Optimistic	60,969	16,470 (27.0)	48,692	33,610 (69.0)	2.56 (2.52–2.59)
	Intermediate A	60,969	3201 (5.3)	48,692	7718 (15.9)	3.02 (2.90–3.14)
	Intermediate B	60,969	6231 (10.2)	48,692	22,244 (45.7)	4.47 (4.36–4.59)
	Pessimistic	60,969	1513 (2.5)	48,692	5339 (11.0)	4.42 (4.18–4.67)
Germany	Optimistic	6876	3786 (55.1)	3042	1938 (63.7)	1.16 (1.12–1.20)
	Intermediate A	6876	326 (4.7)	3042	123 (4.0)	0.85 (0.70–1.04)
	Intermediate B	6876	558 (8.1)	3042	488 (16.0)	1.98 (1.76–2.21)
	Pessimistic	6876	81 (1.2)	3042	58 (1.9)	1.62 (1.16–2.26)
Spain	Optimistic	16,264	8602 (52.9)	12,858	6423 (50.0)	0.94 (0.92–0.97)
	Intermediate A	16,264	375 (2.35)	12,858	275 (2.1)	0.93 (0.80–1.08)
	Intermediate B	16,264	10 (0.1)	12,858	1 (0.0)	0.13 (0.02–0.99)
	Pessimistic	16,264	1 (0.0)	12,858	0 (0.0)	–
UK	Optimistic	92,737	65,317 (70.4)	25,861	19,237 (74.4)	1.06 (1.05–1.06)
	Intermediate A	92,737	2912 (3.1)	25,861	555 (2.1)	0.68 (0.62–0.74)
	Intermediate B	92,737	9396 (10.1)	25,861	3325 (12.9)	1.27 (1.22–1.32)
	Pessimistic	92,737	341 (0.4)	25,861	126 (0.5)	1.33 (1.08–1.62)

n number of prescriptions

Intermediate A: optimistic about duration (if > 7 days' supply), pessimistic about indication (if unknown)

Intermediate B: pessimistic about duration (if > 7 days' supply), optimistic about indication (if unknown)

three labeling requirements from the pre-implementation to post-implementation periods, except for France, where improved compliance with the maximum daily dose from the pre-implementation (38.7%) to the post-implementation period (83.6%) was observed (RR: 2.16; 95% CI 2.14–2.18).

The number of domperidone prescriptions varied by country, except for Spain, between the pre-implementation and the post-implementation periods (Table 3). The proportion of prescriptions with days' supply ≤7 in the pre- versus the post-implementation period was 6.6% versus 3.3% in Belgium, 32.3% versus 59.9% in France, 11.6% versus 21.2% in Germany, 0.2% versus 0.2% in Spain, and 15.8% versus 18.7% in the UK (data not shown). A summary of missing domperidone prescription data on duration and daily dose for the study period at the prescription level and at the patient level is provided in Table 4. The majority of domperidone prescriptions had no missing dose or duration data fields (62.4–98.6%).

3.3 Post-hoc Analysis

At the request of the regulatory authorities, additional post-hoc or sensitivity analyses were conducted for the physician survey. When excluding the physicians who received the DHPC, the proportions of physicians with high knowledge and understanding regarding the recommended changes to the labeling, approved indication, maximum recommended duration of use, the dosing recommendations (when a prescribing guide was available), and the correct maximum dose for adults and adolescents remained high. In addition, using a regression model revealed that the predictors of getting correct responses were country of respondent (Belgium and France), specialty (PCPs), and number of domperidone prescriptions (low frequency of prescribing domperidone).

For the DUS, additional analyses revealed that most patients had a single prescription of domperidone, which would be more consistent with use for acute nausea and vomiting than with use for a chronic condition such as gastric

Table 3 Number and proportion of prescriptions (adults ≥12 years) meeting individual requirements of the revised label by time period (pre-implementation vs. post-implementation) of drug-utilization study (DUS)

Country	Feature	Pre-implementation period		Post-implementation period		Post- vs. pre-implementation period
		Prescriptions (*n*)	Label compliant *n* (%)	Prescriptions (*n*)	Label compliant *n* (%)	Risk ratio (95% CI)
Belgium	Dose ≤10 mg TID	11,627	9914 (85.3)	17,327	15,660 (90.4)	1.06 (1.05–1.07)
	Comedications min	11,348	10,404 (91.7)	16,912	15,445 (91.3)	1.00 (0.99–1.00)
	Comedications max	11,348	10,230 (90.1)	16,912	15,160 (89.6)	0.99 (0.99–1.00)
	Conditions	11,657	11,423 (98.0)	17,368	17,019 (98.0)	1.00 (1.00–1.00)
France	Dose ≤10 mg TID	61,366	23,762 (38.7)	48,876	40,847 (83.6)	2.16 (2.14–2.18)
	Comedications min	61,256	57,249 (93.5)	48,949	46,635 (95.3)	1.02 (1.02–1.02)
	Comedications max	61,256	56,606 (92.4)	48,949	46,369 (94.7)	1.03 (1.02–1.03)
	Conditions	61,848	60,822 (98.3)	49,273	48,523 (98.5)	1.00 (1.00–1.00)
Germany	Dose ≤10 mg TID	6876	6509 (94.7)	3042	2961 (97.7)	1.03 (1.02–1.04)
	Comedications min	6876	6305 (91.7)	3042	2789 (91.7)	1.00 (0.99–1.01)
	Comedications max	6876	6096 (88.7)	3042	2704 (88.9)	1.00 (0.99–1.02)
	Conditions	6876	5744 (83.5)	3042	2579 (84.8)	1.01 (1.00–1.03)
Spain	Dose ≤10 mg TID	18,834	17,584 (93.4)	15,232	14,503 (95.2)	1.02 (1.01–1.03)
	Comedications min	17,753	15,043 (84.7)	13,884	11,875 (85.5)	1.01 (1.00–1.02)
	Comedications max	17,753	13,160 (74.1)	13,884	10,646 (76.7)	1.03 (1.02–1.05)
	Conditions	24,272	22,678 (93.4)	19,834	18,226 (91.9)	0.98 (0.98–0.98)
United Kingdom	Dose ≤10 mg TID	94,170	82,907 (88.0)	26,305	23,776 (90.4)	1.03 (1.02–1.03)
	Comedications min	133,747	121,653 (91.0)	43,915	40,270 (91.7)	1.01 (1.00–1.01)
	Comedications max	133,747	119,364 (89.2)	43,915	39,752 (90.5)	1.01 (1.01–1.02)
	Conditions	135,125	133,667 (98.9)	44,355	44,092 (99.4)	1.00 (1.00–1.01)

Comedications (min): compliant regarding medications contraindicated for concurrent use (optimistic regarding duration if unknown)

Comedications (max): compliant regarding medications contraindicated for concurrent use (pessimistic regarding duration if unknown)

Conditions: compliance regarding diagnosed conditions in which domperidone is contraindicated

n number of prescriptions, *TID* three times daily

Table 4 Summary of missing data for adults (≥ 12 years) in the EMR databases of five European countries [*n* (%)]

Variable	Belgium	France	Germany	Spain	UK
Prescriptions					
Domperidone prescriptions	53,575 (100)	324,213 (100)	27,173 (100)	102,494 (100)	532,884 (100)
Domperidone prescriptions with no missing dose or duration data fields	51,937 (96.9)	319,625 (98.6)	27,173 (100)	64,005 (62.4)	365,830 (68.7)
Domperidone prescriptions missing duration (and cannot be calculated)	1624 (3.0)	3177 (1.0)	–	34,591 (33.7)	162,195 (30.4)
Domperidone prescriptions missing daily dose (and cannot be calculated)	176 (0.3)	2527 (0.8)	–	28,622 (27.9)	162,001 (30.4)
Patients					
Patients with domperidone prescriptions	37,098 (100)	194,118 (100)	9192 (100)	21,173 (100)	109,767 (100)
Patients with ≥ 1 domperidone prescriptions missing no dose or duration data fields	36,413 (98.2)	192,914 (99.4)	9192 (100)	9412 (44.5)	78,766 (71.8)
Patients with ≥ 1 domperidone prescriptions missing duration (and cannot be calculated)	1154 (3.1)	2378 (1.2)	–	12,986 (61.3)	38,612 (35.2)
Patients with ≥ 1 domperidone prescriptions missing daily dose (and cannot be calculated)	156 (0.4)	1883 (1.0)	–	11,019 (52)	38,559 (35.1)

Since a patient can have ≥ 1 prescription, they may be counted in, for example, both the row for having ≥ 1 prescription with complete data *and* one (or more) of the other rows for having ≥ 1 prescription with missing data

n number of prescriptions

dysmotility. Comparing the pre-implementation period with the post-implementation period, the proportion of patients who were prescribed domperidone more than once significantly ($p < 0.05$) increased in Belgium (10.3–13.9%) but decreased in France (17.3% to 12.5%), Germany (37.4% to 28.9%), and Spain (33.8% to 31.7%).

When missing data were excluded from the indications originally coded as "other," the diagnoses most commonly classified as "other" were gastroenteritis in Belgium (60%), France (32%), and Germany (17%) and "unspecified disorder of the stomach" in Spain (17%). To the extent that gastroenteritis was used to describe patients who presented with nausea and vomiting, those prescriptions previously classified into "other" indications actually had the labeled indication. All or most of the remaining prescriptions whose indication was "other" were presumably for off-label indications.

4 Discussion

Results from both the physician survey and DUS were used to evaluate compliance with and effectiveness of the RMM of domperidone in the EU. The physician survey was used as a process indicator to provide insight into physicians' knowledge of the revised label's recommendations (GVP XVI) [13]. The DUS was used as an outcome indicator to provide an overall measure of the level of clinical actions achieved following the implementation of the RMM. The main strength of the design of the DUS was that prescribing patterns could be examined before and after the labeling change.

The physician survey results indicated high awareness of the labeling changes on indication of use, maximum duration, and maximum dose in adults. Of the physicians who were unaware of the dosing requirements, most of them had access to a prescribing guide, but even for those physicians who did not have access to a prescribing guide, the majority were able to correctly identify the maximum daily dose for adults. Few prescribers were aware of the contraindication of domperidone with concomitant use of potent QT inhibitors, or any contraindicated conditions. To complement the survey information, the DUS showed that, in both pre- and post-implementation periods, compliance with the label's maximum dose, contraindicated concurrent medications, and diagnoses that contraindicated domperidone was above 74% in all countries. Comparing the post-implementation to pre-implementation periods, there was little or no improvement in compliance with the indication, the duration of use, and the dose in all countries, except for France where the improvement in compliance with the restricted dose limitation was substantial.

These findings are consistent with the literature. A recent study used a pharmacy claims database to evaluate the impact of labeling changes of domperidone on the prescribing patterns of the drug in Ireland [14]. The study showed a minimal change on the prescribing patterns after the labeling change and, in particular, found no significant change in use of concomitant medicines that are known to increase the risk of QT prolongation.

There were apparent discrepancies between the physician survey and the DUS results. Only a small proportion of physicians were aware of the contraindications in the physician survey, but the proportion of prescriptions in the DUS that were compliant with these contraindications in the post-implementation period was quite high (above 90% in most countries). A possible reason for this is the low prevalence of these contraindications rather than the judicious avoidance of prescribing in the presence of contraindications. This explanation is consistent with the finding that the proportion of prescriptions in compliance with the contraindications was also high in the pre-implementation period.

4.1 Physician Survey

Several study limitations should be mentioned. Selection bias due to the low response rate as well as volunteer bias were possible and could affect the survey results. In addition, recall bias could have been introduced due to the timing of the survey. The physician survey was conducted in 2016, yet it examined the knowledge and awareness of the labeling changes and DHCP that was distributed in 2014. Indeed, 53% of the eligible physicians stated they had not received the DHPC letter. Thus, it is possible that physicians who responded that they had not received the DHPC might have received it but did not remember that. Also, the source of the physicians' awareness and knowledge of the new labeling information, whether the DHPC versus other sources including the labeling, is not clear.

Another limitation is that information bias related to the format or the wording of the questions may have accounted for some the survey results. Questions related to indication, maximum recommended duration of use, and maximum daily dose for adults were characterized by a requirement for a single correct response. These questions were correctly answered by the majority of physicians. When multiple correct responses were used for questions regarding contraindicated concurrent medications and diagnoses, and indications, only a small proportion of physicians responded correctly. The use of a close-ended question with multiple-response design provided an opportunity for respondents to opt for additional responses, thus leading to an incorrect choice. Furthermore, the phrasing of last question relating to indications for which the physicians would prescribe domperidone, could have led the physicians to select the indications for which they would prescribe domperidone instead of selecting the approved indication. It should be noted that this survey was conducted to examine knowledge and awareness of the physicians after the implementation of the RMM. No assessment of these indicators prior to the implementation of the RMM was performed. In the absence of a similar assessment prior to the labeling change it is impossible to assess the extent of the changes from before the RMM to after it.

4.2 Drug Utilization Study

The databases provided detailed information on the prescribed medications but had several important limitations. Medications may not have been taken as prescribed. This may be a particularly important limitation for drugs that are used PRN (pro re nata; when necessary), such as domperidone. Thus, uncertainty regarding the duration of domperidone use arose from two main sources: First, because in some countries, days' supply (used as a proxy for duration of use) was often unknown, and second, even when days' supply was known, actual duration of use was not known because the medication was used as PRN. The days' supply of most domperidone prescriptions was > 7, which may, in some countries, reflect the minimum pack size for domperidone tablets. The smallest pack size marketed in Belgium, France, Germany, and Spain was 30 tablets, whereas the pack size marketed in the UK was ten tablets. Additionally, in some healthcare systems the cost to the patient to fill a prescription for a 30-day supply was the same as the cost for a 7-day supply. Therefore, the actual duration of use was ambiguous for a large percentage of domperidone prescriptions.

In addition, there was uncertainty about the indication, because prescriptions were not always explicitly linked to diagnoses. The wide differences between labeling compliance in the optimistic scenario and in the other scenarios suggest that missing or ambiguous information about indication and duration of use severely limited the ability of the DUS to assess labeling compliance. Other limitations include the possibility of contraindicated conditions or concurrent medications being missed because patients may have been prescribed domperidone by other physicians not captured in the database, concerns about generalizability, and during the pre-implementation period domperidone was available without a prescription.

5 Conclusion

In summary, findings from the physician survey conducted across five EU countries indicated that slightly less than half the physicians recalled receiving the DHPC, but most were aware of the revised product limitations on the indication, duration of use, and maximum dose, and had suboptimal knowledge regarding concomitant use of domperidone with drugs that prolong the QT interval. The DUS findings were inconclusive on effect of the RMM and compliance with labeling change, except for France, which showed improvements across most scenarios. Given the heterogeneity of data and known limitations of both studies, the findings do not support a definitive conclusion on current compliance with the revised labeling of domperidone.

Acknowledgements Ramji Narayanan, ISMPP CMPP™ (SIRO Clinpharm Pvt. Ltd., India) provided writing assistance, funded by Janssen Global Services, LLC, and Bradford Challis, PhD (Janssen Global Services, LLC) provided additional editorial support for the development of this manuscript.

Compliance with Ethical Standards

Ethical approval Ethics committee approval for conducting the physician survey was obtained in each country, wherever applicable, as per the local requirements. For the DUS, ethics committee approval was required and obtained in the UK and Spain and was not required or obtained in the other countries because it was a retrospective database study from anonymized data. The physician survey and the DUS were conducted in accordance with all applicable regulatory requirements.

Funding The physician survey (ENCePP registration number: EUPAS16095) and drug utilization study (ENCePP registration number: EUPAS16062) were funded by Janssen Research and Development, LLC and MAHs involved in the consortium of companies that market domperidone in Europe.

Conflict of interest Daniel Fife, Peter Hu, and Ute Richarz are full time employees of Janssen Pharmaceutical Research, which markets domperidone. As full-time employees they hold stock, stock options, and pension rights from the company. Sigal Kaplan is an employee of Teva Pharmaceutical Industries Ltd. John Waller is a full-time employee of Adelphi Real World, who were commissioned to conduct the physician survey on behalf of Janssen Pharmaceutical Research. Susan A. Oliveria and Syd Phillips are full-time employees of IQVIA, who were commissioned to conduct the DUS on behalf of Janssen Pharmaceutical.

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