Drug Utilisation Study (DUS) Protocol

Title	A Post-Authorisation Safety Study (PASS) to Assess the Effectiveness of the Risk Minimisation Measures of Domperidone – Physician Survey
Protocol Version Identifier	Version 1: 1MAR2016
Protocol Last Version Date	Not applicable
EU PAS Register Number	Study not registered (to be determined)
Active Substance	domperidone
Medicinal Product	domperidone
Product Reference	ATC code:A03FA03
Procedure Number	EMEA/H/N/PSP/J/0016.1
Marketing Authorisation Holder(s)	Janssen Research & Development on behalf of the Domperidone DUS Collaboration Group (a group of all MAHs involved in the Consortium)
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.
Countries of Study	France, Germany, the United Kingdom, Belgium, and Spain
Author	The DUS protocol subcommittee of the Domperidone DUS Collaboration Group

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	Janssen Research & Development on behalf of the Domperidone DUS Collaboration Group
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2. LIST OF ABBREVIATIONS

Abbreviation	Term
ADR(s)	adverse drug reaction(s)
AE(s)	Adverse event(s); adverse experience(s)
CHMP	Committee for Human Medicinal Products
CI	confidence interval
CRO	Contract research Organisation
DHPC	Direct Healthcare Professional Communication
DUS	Drug Utilisation Study
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
GERD	gastro-oesophageal reflux disease
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Guideline on Good Pharmacovigilance Practice
HCP(s)	Health Care Provider(s)
ICSR	Individual Case Safety Reports
ISPE	International Society for Pharmacoepidemiology
MAH(s)	Marketing Authorisation Holder(s)
OTC	over-the-counter
PASS	Post-authorisation Safety Study
PCP(s)	Primary Care Provider(s)
PhVWP	Pharmacovigilance Working Party
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
SmPC	Summary of Product Characteristics
TID	three times daily

3. RESPONSIBLE PARTIES

The main responsible parties are presented in Table 1.

Table 1: List of All Main Responsible Parties

Responsible Party	Name and Affiliation
Consortium	Domperidone DUS Collaboration Group (for full membership, please refer to Appendix A.
Sponsor	Janssen Research & Development on behalf of the Domperidone DUS Collaboration Group (a group of all MAHs involved in the Consortium)
Principal Investigator	to be determined
Coordinating Investigator	to be determined

4. ABSTRACT

Title of Study: A Post-Authorisation Safety Study (PASS) to Assess the Effectiveness of the Risk Minimisation Measures of Domperidone

Rationale and Background

Pursuant to this Article 31 procedure, the Pharmacovigilance Risk Assessment Committee (PRAC) 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. PRAC also recommended that following the distribution of the DHPC, a Drug Utilisation Study (DUS) should be conducted to assess the effectiveness of risk minimisation measures and to monitor off-label use. Following discussion with health authorities, the study will be conducted as a joint effort of Marketing Authorisation Holders (MAHs) who agreed to participate in the consortium for domperidone.

Research Question and Objectives

Primary objective:

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, 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 is a multi-national, non-interventional cross-sectional study. A physician survey has been developed to be 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 SmPC and the distribution of DHPC. The study is to be implemented across 5 EU countries with varying prescription volumes: France, Germany, the United Kingdom, Belgium, and Spain. Data for the survey will be collected electronically via the internet.

Population

The study population will be comprised of health practitioners specialised in the following 5 areas of medicine: primary care practice (general practice and internal medicine),

gastroenterology, obstetrics/gyneacology, neurology, and paediatrics. This population of prescribers was chosen for their potential to prescribe domperidone more frequently for the approved label or off-label indications.

Variables

The primary study endpoint is the physician knowledge and understanding of the new safety information for domperidone, as detailed in the SmPC and DHPC. This study is designed to evaluate physician knowledge and understanding of the new safety information for domperidone, as detailed in the Summary of Product Characteristics (SmPC) and DHPC. Evaluations include indications for domperidone prescribing, length of treatment, maximum daily dose, concomitant use of domperidone, contraindicated conditions, and treated population characteristics. An additional variable will capture the prescribing behaviour of domperidone for off-label indications.

In addition, prescriber characteristic data will be collected on the prescribers including age, sex, specialty, clinical practice type, and country.

Data Sources

The survey will be conducted using a multiple choice survey (Appendix C) via the internet to address the most important safety information in the DHPC and potential off-label use. The survey will be translated into the local language in each country and will be administered to Health Care Providers (HCPs) across 5 EU countries.

Study Size

A total sample size of 1,830 respondents is required assuming that 60% of the answers for each question are answered correctly. A sample size of 366 respondents in each country produces a two-sided 95% confidence interval (CI), constructed using score (Wilson) method, with a width of 10%.

In countries with a paediatric indication for domperidone, each speciality will account for approximately 1/5 of the responders. In countries without a paediatric indication, the remaining 4 specialties will be sampled.

Data Analysis

Descriptive statistics will be used for evaluation and comparison of prescriber knowledge and awareness as measured by the study survey. The study population will be described using demographic characteristics, such as age, sex, specialty, clinical practice type, and country. Continuous variables will be presented using appropriate descriptive statistics, such as mean, median, standard deviation and range. Categorical variables will be described using frequencies. Further stratification by baseline variables may be performed and will be described in the statistical analysis plan. With the exception of Questions 3 and 4 in Part II, each individual question in Part II will be described using the following categories: ‘Correct’; ‘Incorrect’; or ‘Not answered.’

Point estimate and 95% confidence interval (CI) of percent of HCPs with correct responses to each question will be calculated. The primary analysis will present the rate of correct answers for

all countries pooled together. A secondary analysis will present the rates of correct answers by country.

Milestones

Milestone	Planned Date
DHPC distribution	AUG-DEC2014
Start of data collection	4 months after approval of the protocol by Health Authorities
End of data collection	4 months after start of data collection
Study progress report	Not applicable
Interim report	Not applicable
Registration in the EU PAS register	Before the start of data collection
Final report of study results	6 months after the end of data collection

5. AMENDMENTS AND UPDATES

None; this is the first PRAC-endorsed version of the protocol.

6. MILESTONES

After the DHPC has been sent out in all target countries and after obtaining approval by the Pharmacovigilance Risk Assessment Committee (PRAC), the survey will start within 4 months, and data will be collected for a period of 4 months. A final report on the investigation will be provided to PRAC 6 months after the end of data collection.

Study milestones are presented in Table 2.

Table 2: Study Milestones

Milestone	Planned Date
DHPC distribution	AUG-DEC2014
Start of data collection	4 months after approval of the protocol by Health Authorities
End of data collection	4 months after start of data collection
Study progress report	Not applicable
Interim report	Not applicable
Registration in the EU PAS register	Before the start of data collection
Final report of study results	6 months after the end of data collection

7. RATIONALE AND BACKGROUND

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 European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) initiated a review of domperidone-containing medicines at the request of the Federal Agency for Medicines and Health Products (FAMHP), under Article 31 of Directive 2001/83/EC over concerns about cardiac adverse effects of domperidone. Subsequently, the PRAC recommended that the product label (Summary of Product Characteristics/SmPC and Patient Information Leaflet/PIL) of domperidone-containing medicines be updated to strengthen the information regarding cardiac risks. In addition, 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 gastro-oesophageal reflux disease (GERD), for the treatment of diabetic and non-diabetic gastroparesis, and for the treatment of symptoms of postural hypotension in Parkinson's patients.

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

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

The CHMP continues to support a positive risk-benefit balance for domperidone provided that the drug is used according to the new label. Within the context of risk minimisation measures, the 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.

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. PRAC also recommended that following the distribution of the DHPC, a Drug Utilisation Study (DUS) should be conducted to assess the effectiveness of risk minimisation measures and to monitor off-label use. Following discussion with health authorities, the study will be conducted as a joint effort of Marketing Authorisation Holders (MAHs) who agreed to participate in the consortium.

8. RESEARCH QUESTION AND OBJECTIVES

The study uses a rigorous cross-sectional survey method for 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.

Primary objective:

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, 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.

9. RESEARCH METHODS

9.1. Study Design

This is a multi-national, non-interventional cross-sectional study. A physician survey has been developed 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 will be collected electronically via the internet.

A survey is proposed to establish whether the intervention, which occurred in the past, has been effective and the physicians have adequately understood the new safety information for domperidone and to develop corrective actions, if necessary. Surveys are useful and frequently used as a systematic method for primary data collection to assess the effectiveness of risk minimisation. Moreover, data are collected and captured for the purpose of the specific research question and thus enable tailoring the survey to the specific study objectives. The nature of the survey also allows for capturing of data that are not necessarily available from other data sources, including obtaining 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. Finally, the survey will examine whether respondents prescribe domperidone for selected conditions that are not labelled.

The study is to be implemented in 5 EU countries: France, Germany, the United Kingdom, Belgium, and Spain. It is of note that the planned list of participating countries may be subject to modifications, according to agreement with the local health authorities regarding the distribution of the DHPC in the concerned countries and any change in the use of the product.

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. Though retrospective data on prescription dispensing from healthcare databases seems the most obvious and direct approach for measuring adherence to the new domperidone label, this approach has several important limitations. Most of the outcomes of interest for this DUS, including indication, dose, and duration of use are not directly recorded in healthcare databases and could only be estimated based on assumptions that may not always hold true. For example, diagnoses and medications captured in these databases do not typically include explicit links between them, so the indication for prescribing the drug is often ambiguous or unknown. In addition, assessing dose and duration of use in healthcare databases is challenging for

medications prescribed for use as needed, such as domperidone and thus, estimation of these variables may be questionable. Moreover, this uncertainty about duration of use carries uncertainty about concurrent use with contraindicated medications. Other possible approaches for assessing drug-use patterns were also considered, including chart review or patient interviews. Either of these approaches would create burden on patients and physicians as it would require obtaining patient consent, and cooperation from the prescribing physicians to make the charts accessible, or require the sponsor to contact the patients who received domperidone prescriptions. In addition, either of these designs would be subject to volunteer bias, and neither of these designs assures that information on drug utilisation has been recorded and could be obtained. Charts often have an appreciable rate of missing information that could affect the variables of interest. Furthermore, obtaining information from patients could have other major limitations related to recall bias. The extent of this recall bias may be appreciated from the practice of a US national interview survey of health events. 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.

9.2. Study Setting and Population

The study population will be comprised of healthcare practitioners specialising in the following 5 areas of medicine: primary care practice (general practice and internal medicine), gastroenterology, obstetrics/gyneacology, neurology, and paediatrics. These eligible physicians will be further screened through the study survey to determine their inclusion in the study. Physicians will be included in the study if they prescribe or plan to prescribe domperidone.

This 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 is expected for the following indications: treatment of GERD, dyspepsia, inflammatory bowel disease (IBD), 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 survey is designed to be implemented during a 4-month period and collect data via the internet from the core prescriber groups in 5 European countries. The distribution of contacted physicians by specialty will be based on the estimated domperidone prescribing patterns in each country.

The sampling frame of prescribers in the participating countries will be identified from a market research database of Health Care Providers (HCPs). From this sampling frame, a random sample of physicians will be invited to participate according to their specialty. A comparison between responding and non-responding physicians will be examined. A letter to the identified prescribers will be sent to inform them about the study and to provide them with the link to the online survey. In addition, prescribers will be recruited using various methods including letter, telephone call, electronic mail, and other methods. It is planned to recruit a total of 1,830 prescribers in 5 countries.

Prescribers' knowledge and awareness are expected to vary by country by practice and by specialty. For that reason, information will be collected regarding the physician specialty and country. Efforts will be made to collect a balanced and representative sample of prescribers of all specialties in each country.

Given implementation of the survey in 5 countries, approximately 366 prescribers will be recruited in each country. The study intends to collect data from a similar number of prescribers in each country. Prescribers will be compared to examine differences in awareness and knowledge within country and across specialty.

The survey will assess the prescriber eligibility to complete the survey by checking whether s/he prescribes domperidone. If not prescribed, the prescriber will be asked if s/he prescribed this product in the past.

To provide an empirical estimate of the enrolled sample representativeness, a register for all eligible physicians will be established. The register will include physicians who were identified to participate in the survey according to their specialty and were invited to participate in the study. The register will collect information from both participating and non-participating physicians who were identified and include the following information, if available: age, sex, specialty, and clinical practice type, and country. This register will provide some insight on participation rates and potential selection bias. A comparison between responding and non-responding physicians will be examined.

9.3. Variables

Information about the study participants and their knowledge will be extracted from the survey. The key indicators for the effectiveness of the risk minimisation measures of domperidone will be assessed using process indicators. Specifically, the physicians will be 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
- overall benefit-risk ratio of domperidone

The primary study endpoint is the physician knowledge and understanding of the new safety information for domperidone, as detailed in the SmPC and DHPC. This study is designed to evaluate physician knowledge and understanding of the new safety information for domperidone, as detailed in the Summary of Product Characteristics (SmPC) and DHPC. Evaluations include indications for domperidone prescribing, length of treatment, maximum daily dose, concomitant use of domperidone, contraindicated conditions, and treated population characteristics. An additional variable will capture the prescribing behaviour of domperidone for off-label indications.

With the exception of Questions 3 and 4 in Part II, adequate knowledge and understanding will be defined as a correct answer to the question (dichotomous variable).

In addition, in Part I of the survey, prescriber characteristic data will be collected including, age, sex, specialty, clinical practice type, and country.

9.4. Data Sources

The survey will be 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 will be translated into the local language in each country and will be administered to HCPs across 5 EU countries.

The survey will include questions on physician or practice characteristics, eligibility screening questions, and knowledge, and understanding questions. The survey will include mostly closed-ended questions with multiple choice answer options only (to minimise error and interpretability error), and will take approximately 10 minutes to complete. E-mails will be sent to all physicians in the study sample who are potential prescribers, and up to 3 telephone calls will be made to non-respondents. A two-part survey was developed to address the most important safety information in the DHPC and potential off-label use (Appendix C.1).

Part I of the survey will establish whether or not physicians met the criteria for inclusion in the analysis of survey data and solicits information about the physician's demographic characteristics and practice. Part II contains multiple choice questions to collect information on the awareness of the changes to the SmPC, and specifically regarding indications for domperidone prescribing, length of treatment, maximum daily dose, concomitant use of domperidone, contraindicated conditions, treated population characteristics, and potential off-label use.

The survey will be conducted by an independent contract research organisation (CRO).

The survey will be tested after obtaining responses from approximately 5% of physicians in each country. The purpose of this test is to assess clarity of the questions, comprehension and acceptability of the designed instrument. In case revisions to the survey are required, a revised version of the survey will be issued and the study protocol will be updated.

9.5. Study Size

Sample size determination is based on consideration to provide accurate estimate of percentage of physicians answering each question correctly. The table below summarises the sample size required for different observed sample proportion, when two-sided 95% confidence interval (CI), with a width of 10%, is constructed using score (Wilson) method.

Observed sample proportion	Sample size
50%	381
60%	366
70%	320

A required sample of 366 physicians in each country will be included. Therefore, an overall number of 1,830 physicians in 5 participating countries will be recruited. In countries with a paediatric indication for domperidone, each speciality will account for approximately 1/5 of the responders. In countries without a paediatric indication, the remaining 4 specialties will be sampled.

9.6. Data Management

Data will be collected using an on-line survey, which will be provided and maintained by a Contract Research Organisation (CRO). The CRO will be responsible for the secure data storage and management, while complying with local and global regulatory guidelines. In addition, the CRO will be responsible for the accuracy, quality, and consistency of the data. All personnel handling and managing data will be provided with individual system access rights. The access to data will be controlled by different password-protected authorization levels given to principal investigator, system administrator, and data managers.

9.7. Data Analysis

Descriptive statistics will be used for evaluation and comparison of prescriber knowledge and awareness as measured by the study survey. The study population will be described using demographic characteristics, such as age, sex, specialty, clinical practice type, and country. Continuous variables will be presented using appropriate descriptive statistics, such as mean, median, standard deviation and range. Categorical variables will be described using frequencies. Further stratification by baseline variables may be performed and will be described in the statistical analysis plan.

Part II, Questions 1, 2, 5, 6, 7, 8, and 9 of the survey will be scored as 'Correct,' 'Incorrect,' or 'Not answered.' Each question will be analysed separately for the proportion of HCPs with correct answers.

The primary analysis will present the rate of correct answers per question for all countries pooled together. An additional analysis will include the rates of correct answers by country. The proportion of physicians who potentially prescribe domperidone for unapproved indications will be described.

In order to address a possible selection bias in the HCPs responding to the survey, the demographic characteristics of responders will be compared with those of non-responders (HCPs contacted for the survey but not responding).

9.8. Quality Control

Given that all interviews will be conducted online, the survey will be scripted to ensure that the data delivered is clean and free of errors. This also ensures that no interviewer bias will affect the quality of the interviews.

In order to guarantee the identity of the physicians, surveys will be considered non-valid if Part I (physician characteristics and screening) is not filled in.

9.9. Limitations of the Research Methods

This survey consists of a large sample of physicians who will be surveyed to examine their knowledge and understanding with regard to the new labeling for domperidone. The survey will be conducted among several specialties and several countries. The survey will be tested after obtaining responses from approximately 5% of physicians in each country to assess the clarity of the survey.

In addition, an increased sample size and use of various recruitment techniques will be used in order to increase the response rate. In order to overcome the potential limitation that the proposed study may have a low response rate by physicians invited to participate in the survey, the CRO will contact as many HCPs as needed to achieve the target number of usable completed questionnaires, i.e., 369 completed questionnaires in each country involved in the study. In order to increase the participation rate, the invitation to participate in the survey will be sent repeatedly, with several periodical reminders. In addition, the survey will consist of short and self-explanatory questions, not burdened by additional materials or instructions. This should facilitate the process of participation in the study and increase the number of valid surveys filled by the study population. As with most surveys, the sampling frame and the recruitment of participants may introduce selection bias and may influence the representative of the study population. In order to minimise such selection bias, the following aspects will be considered and addressed in the study, including attempt to use a large sampling frame, taking into account physician's specialty, country, and other characteristics. An attempt will be made to have a heterogeneous sample of physicians with appropriate diversity to allow stratification by key characteristics. Furthermore, the demographic characteristics of responders will be compared with those of non-responders (HCPs contacted for the survey but not responding).

Since participation in the study is voluntary, the final sample of physicians may also be subject to selection bias. To overcome this limitation, the data collection process will be monitored for the distribution of different medical specialists responding to the survey. Using this risk-based monitoring approach, reminders will be sent out proportionally to the specialties underrepresented in the survey. This process will be reiterated in an attempt to achieve a target number of surveys for each country, with a balanced representation of primary care practice physicians (general practice and internal medicine), gastroenterologists, obstetricians/gynaecologists, neurologists, and paediatricians.

In addition, the study is planned to maintain a register of all eligible physicians who were contacted and did not respond to the study. To address the extent of selection bias, these non-responding physicians will be compared to the responding physicians, using background characteristics, such as physicians' age, sex, specialty, clinical practice type, and country to evaluate potential influences on the representativeness of the sample.

It is probable that more physicians who actually prescribe domperidone participate in the survey than those who never prescribe the drug, because the regular prescribers feel more familiar with the drug. This may lead to an overestimation of off-label use, especially in obstetrics/gynaecologists and neurologists as these specialties probably rarely prescribe a drug for short-term nausea and vomiting.

9.10. Other Aspects

Protocol Revision

Any eventual amendment to the study protocol will be previously agreed between the MAHs participating in the Consortium and jointly approved. The written amendment will be provided to the PRAC.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Ethics Committee and Research Approval

Ethical approval will be sought according to local regulations.

The study may start only when the written endorsement from the PRAC has been issued and the Competent Authorities of the member states in which the study will be conducted have received the study protocol, in accordance with GVP VIII C4.1.

The study will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE, 2007) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2012). The proposed study is an observational study and will comply with the definition of non-interventional studies provided in Article 2(c) of Directive 2001/20/EC (European Commission, 2008) and the 2013 Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorization Safety Studies (EMA, 2013, Module VIII).

10.2 Data Protection

All data will be anonymised and recorded into a secure study database. The access to the database will be controlled by different password-protected authorization levels given to investigators, data managers and database administrators. The study database will be maintained and secured as requested by the local privacy regulations of countries participating in the study. Processes assuring data security will be employed during data collection, storage and back-up. The data and all study-related documents will be kept until sponsor's written notification that records may be destroyed. No HCP data will be identifiable to the MAHs.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

During recruitment for and conduct of the DUS a participating physician may report adverse events (as defined in the Guideline on Good Pharmacovigilance Practices Module VI – Management and reporting of adverse reactions to medicinal products) on domperidone or any other product to the CRO. Therefore, the CRO will be trained on adverse event reporting according to the sponsor's requirements (as defined, the sponsor is Janssen Research & Development on behalf of the Domperidone DUS Collaboration Group).

The CRO will review/monitor completed adverse events (AEs) daily and forward each AE received from questionnaires and any AE received from other sources (e.g., telephone call with HCP, electronic mail) to the MAH responsible for the product, as well as each AE with an unidentifiable MAH to applicable MAH(s) who have product market authorisation in the concerned country, by completing the national AE/ADR reporting form and sending by fax or email, within 24 hours of the receipt. The same applies to any reported special case situations as well as to information concerning exposure (maternal or paternal) during pregnancy or breastfeeding.

MAH responsibilities for management of Adverse Event reports as per EU legislative requirements

All AEs reported in connection with the study related to domperidone will be regarded as solicited. Any adverse reactions which are suspected to be related to product other than domperidone will be classified and reported as spontaneous Individual Case Safety Reports (ICSRs).

According to GVP VI.C.1.2., an adverse event should be classified as an adverse reaction if there is at least a reasonable possibility of causal relationship. Only valid ICSRs of adverse reactions, which are suspected to be related to any product by the healthcare professional or the Sponsor, will be reported to Health Authorities. Other reports of adverse events will be summarised in the final study report.

According to GVP VI.B.6.3., reports of overdose, lack of efficacy, abuse, off-label use, misuse, medication error or occupational exposure with no associated adverse reaction should not be reported as ICSRs to Health Authorities. These reports without drug-related AE will be summarised in the final study report provided by the CRO and will be referred in the PSURs. All special situation reports with drug-related AEs will be submitted to the Health Authorities.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study Final Clinical Report will be issued in accordance with the ICH E3 guidance (July 1996) regarding the "Structure and Content of Clinical Study Reports".

APPENDIX A. LIST OF STAND-ALONE DOCUMENTS

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

Document Number 1: List of Companies Participating in the Domperidone DUS Collaboration Group		
Parent Company	**MAH**	**MAH Address**
Johnson & Johnson	Janssen-Cilag Pharma Gmbh	Vorgartenstraße 206B, AT-1020 Vienna Austria
Johnson & Johnson	Johnson & Johnson Consumer NV/SA	Antwerpseweg 15-17, 2340, Beerse, Belgium
Johnson & Johnson	Johnson & Johnson, Prodaja Medicinskih In Farmacevtskih Izdelkov, D.O.O.	Smartinska cesta 53, SI-1000, Ljubliana, Slovenia
Johnson & Johnson	Janssen-Cilag International NV	Turnhoutseweg 30, 2340, Beerse, Belgium
Johnson & Johnson	Janssen-Cilag s.r.o.	Karla Engliše 3201/6, 150 00 Prague 5
Johnson & Johnson	Janssen-Cilag A/S	Hammerbakken 19, DK-3460 Birkerød, Denmark
Johnson & Johnson	Janssen-Cilag S.A.	Paseo de las Doce Estrellas, 5-7, 28042 Madrid, Spain
Johnson & Johnson	Janssen-Cilag	1, rue Camille Desmoulins, TSA 91003, 92787 Issy Les Moulineaux, Cedex 9, France
Johnson & Johnson	Johnson & Johnson Hellas Consumer AE	Aegialias & Epidavrou 4, 15125, Maroussi, Athens, Greece
Johnson & Johnson	Janssen-Cilag Kft.	H-2045, Törökbálint, To Park, Hungary
Johnson & Johnson	McNeil Healthcare (Ire) Ltd	Airton Road, Tallaght, Dublin 24, Ireland
Johnson & Johnson	Janssen-Cilag Spa	Via M.Buonarroti, 23, I-20093 Cologno Monzese, Italy
Johnson & Johnson	UAB „Johnson & Johnson“	Geležinio Vilko g. 18A, LT-08104 Vilnius, Republic of Lithuania
Johnson & Johnson	Johnson & Johnson Consumer NV/SA	Antwerpseweg 15-17, 2340, Beerse, Belgium
Johnson & Johnson	Johnson & Johnson Consumer B.V.	Roosveltweg 15, 1314 SJ Almere
Johnson & Johnson	Johnson & Johnson s.r.o	Karadžičova 12, 821 08 Bratislava, Slovak Republic
Johnson & Johnson	Johnson & Johnson, Lda.	Estrada Consiglieri Pedroso, 69 A - Quelez de Baixo, 2730-055 Barcaerna, Portugal
ABC Farmaceutici	ABC Farmaceutici S.p.A.	Corso Vittorio Emanuele II, 72 – 10121 – Turin, Italy
Actavis Group PTC	Actavis Group PTC ehf.	Reykjavikurvegur 76-78 - 220 Hafnarfjördur - Iceland
Angenerico	Acraf S.p.A.	Viale Amelia 70 – 00181 Rome – Italy
Aurobindo Pharma	Actavis BV	Baarnsche Dijk 1, Postbus 313 – 3740 AH Baarn – The Netherlands
Aurobindo Pharma	Alternova A/S	GL. Torv 2 – 5800 Nyborg – Denmark
Aurobindo Pharma	Arrow Génériques SAS	26 Av. Tony Garnier – 69007 Lyon - France
Aurobindo Pharma	Aurovitas Unipessoal Lda	Rua Virgilio Correia 11 A – 1600-219 Lisboa - Portugal
Aurobindo Pharma	Milpharm Ltd	Ares Block, Odyssey Business Park, West End Road, South Ruislip – Middlesex HA4 6QD – United Kingdom
Aurobindo Pharma	Pharmacin BV	Molenvliet 103 – 3335 LH Zwijndrecht – The Netherlands
Aurobindo Pharma	Sofar SpA	Via Firenze 40 – I-20060 Trezzano Rosa - Italy

Document Number 1: List of Companies Participating in the Domperidone DUS Collaboration Group		
Parent Company	**MAH**	**MAH Address**
Azevedos	Laboratórios Azevedos – Indústria Farmacêutica SA	Estrada Nacional 117-2, Edificio Azevedos, Alfragide – 2614-503 Amadora - Portugal
Betapharm Arzneimittel	Betapharm Arzneimittel GmbH	Kobelweg 95 - 86156 Augsburg - Germany
Biogaran	Biogaran	15 Boulevard Charles de Gaulle - 92707 Colombes Cedex - France
Bristol Laboratories	Bristol Laboratories Limited	Unit 3, Canalside Northbridge Road – Berkhamsted, Hertfordshire HP4 1EG - United Kingdom
Co-Pharma	Co-Pharma Ltd	Unit 4, Metro Centre, Tolpits Lane – Watford, Herts – WD18 9SS – United Kingdom
Cristers	Cristers SAS	22, Quai Galliéni – 92150 Suresnes – France
DOC Generici	DOC Generici Srl	Via Turati 40 – 20121 Milan – Italy
Esteve	Laboratorios del Dr. Esteve SA	Av. Mare de Deu de Montserrat 221 – 08041 Barcelona – Spain
Focus Pharmaceuticals	Focus Pharmaceuticals Ltd.	Unit 5 Faraday Court, First Avenue, Centrum 100 – Burton upon Trent, Staffordshire, DE14 2WX – United Kingdom
Generis Farmacêutica	Generis Farmacêutica SA	Rua João de Deus, 19 - 2700-487 Amadora - Portugal
Giuliani Pharma	Giuliani SpA	Via Palagi 2 – 20129 Milan - Italy
Hexal	Hexal AG	Industriestr. 25 - 83607 Holzkirchen - Germany
Hexal	1 A Pharma GmbH	Keltenring 1 + 3 – 82041 Oberhaching – Germany
Hexal	Rowex Ltd	Bantry, Co. Cork - Ireland
Hexal	Sandoz S.A.S.	49, avenue Georges Pompidou - 92300 Levallois-Perret – France
Hexal	SANDOZ SpA	Largo Umberto Boccioni 1 - 21040 Origgio – Varese - Italy
Hexal	Sandoz BV	Veluwezoom 22 -1327 AH Almere - The Netherlands
Italchimici	Italchimici S.p.A.	Via Pontina 5, km 29 - 00040 Pomezia (RM) - Italy
Kela Pharma	Kela Pharma NV	Industriepark West 68 – 9100 Sint-Niklaas - Belgium
Labesfal Genéricos	Labesfal Genéricos SA	Av. Dr. Afonso Costa, n° 1370 – 3465-051 Campos de Besteiros – Portugal
Laboratoire Gerda	Gerda Laboratoires SAS	24 rue Erlanger – 75016 Paris – France
Laboratório Medinfar – Produtos Farmacêuticos	Genéricos Portugueses Lda.	Rua Henrique de Paiva Couceiro, 29 Venda Nova - 2700-451 Amadora – Portugal
Laboratório Medinfar – Produtos Farmacêuticos	Laboratório Medinfar - Produtos Farmacêuticos SA	Rua Manuel Ribeiro de Pavia, 1 - 1º, Venda Nova - 2700-547 Amadora – Portugal
Manx Healthcare	Manx Healthcare Limited	Taylor Group House, Wedgnock Lane - Warwick CV34 5YA – United Kingdom
MEDA	MEDA Pharma S.L.	Av. Castilla 2 (Edif. Berlin 2ª Pl) - 28830 San Fernando de Henares - Spain

Document Number 1: List of Companies Participating in the Domperidone DUS Collaboration Group		
Parent Company	**MAH**	**MAH Address**
Mylan EMEA	Mylan SPRL	Park Rozendal, Terhulpsesteenweg 6A – 1560 Hoeilaart - Belgium
Mylan EMEA	Mylan SAS	117 Allée des Parcs – F 69792 Saint-Priest Cedex - France
Mylan EMEA	Mylan SpA	Via Vittor Pisani 20 – 20124 Milan – Italy
Mylan EMEA	Mylan BV	Dieselweg 25 – NL-3752 LB Bunschoten – The Netherlands
Mylan EMEA	Mylan Lda	Parque Expo, Edifício Atlantis, Avenida D. João II, Lote 1.06.2.2 C - 7.3 e 7.4 - 1990-095 Lisbon - Portugal
Pensa Pharma	Pensa Pharma SpA	Via Ippolito Rosellini 12 – 20124 – Milan - Italy
Pensa Pharma	Pensa Pharma SA	C/ Jorge Comín (médico pediatra) 3 - 46015 Valencia– Spain
Pensa Pharma	TOLIFE Produtos Farmacêuticos S.A.	Avenida do Forte nº 3, Edifício Suécia IV, Piso 0 - 2794-093 Carnaxide - Portugal
Pierre Fabre	Pierre Fabre Médicament SAS	45 place Abel Gance – 92100 Boulogne – France
Pierre Fabre	Pierre Fabre Farmaka AE	Mesogeion AV 350, Agia Paraskevi – 15341 Athens - Greece
Pierre Fabre	Pierre Fabre Pharma Srl	Via Winckelmann 1 - 20146 Milan - Italy
Ranbaxy	Terapia SA	Str. Fabricii nr. 124 - Cluj Napoca - Romania
S.F. Group	S.F. Group Srl	Via Beniamino Segre, 59 - 00134 - Rome - Italy
Sanofi-Aventis France	Sanofi-Aventis France	1-13 Boulevard Romain Rolland – 75014 Paris – France
Winthrop Pharmaceuticals UK Ltd trading as Zentiva	Winthrop Pharmaceuticals UK Limited	One Onslow Street, Guildford - Surrey GU1 4YS - United Kingdom
STADA	ALIUD PHARMA GmbH - Laichingen	Laichingen, Germany
STADA	Centrafarm BV	Nieuwe Donk 3 - 4879 AC Etten-Leur - The Netherlands
STADA	Ciclum Farma Unipessoal Lda	Paco de Arcos - Portugal
STADA	Crinos SpA	Milan - Italy
STADA	EG SpA	Milan - Italy
STADA	EG LABO Laboratoires EuroGenerics	Boulogne-Billancourt Cedex - France
STADA	Eurogenerics NV/SA	Brussels - Belgium
STADA	Healthypharm BV	Etten-Leur - Netherlands
STADA	Stada Arzneimittel AG	Stadastrasse 2-18 - 61118 Bad Vilbel – Germany
STADA	Stada GmbH	Stadastr. 2-18 - 61118 Bad Vilbel – Germany
Takeda	Takeda GmbH	Byk-Gulden-Str. 2 - 78403 Konstanz - Germany
Teva	AbZ-Pharma GmbH	Graf-Arco-Str. 3 - 89079 Ulm - Germany
Teva	Mediq Farma B.V	Hertogswetering 159 - 3543 AS Utrecht - The Netherlands
Teva	Pharmachemie BV	Swensweg 5 - Haarlem 2031 GA - The Netherlands

Document Number 1: List of Companies Participating in the Domperidone DUS Collaboration Group		
Parent Company	**MAH**	**MAH Address**
Teva	Ratiopharm GmbH	Graf-Arco-Str. 3 - 89079 Ulm - Germany
Teva	Ratiopharm Lda	Lagoas Park, Edifício 5 A, Piso 2 - 2740-245 Porto Salvo – Portugal
Teva	Teva Pharma Belgium NV	Laarstraat 16 - 2610 Wilrijk – Belgium
Teva	Teva GmbH	Graf-Arco-Str. 3 - 89079 Ulm - Germany
Teva	Teva Italia Srl	Via Messina, 38 - 20154 Milan – Italy
Teva	Teva Nederland BV	Swensweg 5 - Haarlem 2031 GA - The Netherlands
Teva	Teva Pharmaceuticals Europe BV	Piet Heinkade 107 - 1019 GM Amsterdam - The Netherlands
Teva	Teva Santé SAS	100-110 Esplanade du General de Gaulle - 92931 La Defense Cedex - France
ZYDUS France	ZYDUS France SAS	ZAC des Hautes Pâtures, 25, rue des Peupliers, Bât. L – 92752 Nanterre Cedex - France

APPENDIX B. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

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

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

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

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

Study title:

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

Study reference number:

To be determined

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	7,9
1.1.2 End of data collection[2]	☒	☐	☐	7,9
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	7,9
1.1.6 Final report of study results.	☒	☐	☐	7,9

Comments:

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	5,11,12
2.1.2 The objective(s) of the study?	☒	☐	☐	5,12
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	5-6,13
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	5,13
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	5,12
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	5-6,13
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	5,7
4.2.2 Age and sex?	☒	☐	☐	13,14
4.2.3 Country of origin?	☒	☐	☐	5,13
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	14

Comments:

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

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	6,15-16
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

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

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	6,15
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	6,15-16
8.1.3 Covariates?	☒	☐	☐	6,15-16
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	6,15-16
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	6,15-16
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	6,15-16
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	6,17

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	6,17-18
10.3 Are descriptive analyses included?	☒	☐	☐	6,17-18
10.4 Are stratified analyses included?	☒	☐	☐	6,7,17-18
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	6,7,17
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	17,20
11.3 Are methods of quality assurance described?	☒	☐	☐	17
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	13-14,20
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	13-14,20
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	17
12.3 Does the protocol address other limitations?	☒	☐	☐	19-20

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	21
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	21
13.3 Have data protection requirements been described?	☒	☐	☐	21

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	8

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	23
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	23

Name of the main author of the protocol: _____

Date: / /

Signature: _____

APPENDIX C. ADDITIONAL INFORMATION

APPENDIX 1. PHYSICIAN SURVEY

Effectiveness Testing of the DHPC on Domperidone-containing Products

Survey for Physicians

PART I: Demographics and Screening for Eligibility

1. What is your primary medical specialty?
   a. Primary Care Provider (general practice or internal medicine)
   b. Gastroenterologist
   c. Obstetrician/Gynaecologist
   d. Neurologist
   e. Paediatrician
   f. Other (please specify): _____
2. Please indicate the country of your practice:
   a. France
   b. Germany
   c. United Kingdom
   d. Belgium
   e. Spain

3. Your practice is primarily:
    a. Primary care
    b. Specialist ward
    c. Academic institution
    d. Secondary care
    e. Outpatient care
    f. Other (please specify): _____

4. Your age (in years) is:
    a. 20-29
    b. 30-39
    c. 40-49
    d. 50-59
    e. 60+

5. Your sex is:
    a. Male
    b. Female

6. Have you received the Dear Healthcare Professional Communication (DHPC) on the use of domperidone dated 2014-2015?
    a. No
    b. Yes

7. If the answer to Question 6 was No, have you prescribed domperidone products in the last 6 months?

    a. No

    b. Yes

8. If the answer to Question 6 was Yes, have you prescribed domperidone products since receiving the DHPC?

    a. No

    b. Yes

9. Approximately how many prescriptions have you written for domperidone in the last 30 days?

    a. 0 prescriptions

    b. 1-5 prescriptions

    c. 6-10 prescriptions

    d. 11-20 prescriptions

    e. 21 or more prescriptions

PART II: Questions Concerning Domperidone-containing Products

1. What is an approved indication of domperidone?
   a. Dyspepsia
   b. Nausea and vomiting
   c. Reflux esophagitis

2. What is the maximum recommended usual duration of use?
   a. 7 days
   b. 30 days
   c. No limitation

3. Do you readily know the dosing recommendations?
   a. Yes
   b. No

4. If the answer to Question 3 is no, do you have access to a prescribing guide?
   a. Yes
   b. No

5. What is the maximum daily dose for adults and adolescents (12 years of age and older and weighing 35 kg or more)?

   a. 80 mg per day (20 mg QID)

   b. 30 mg per day (10 mg TID)

   c. 10 mg per day (10 mg QD)

6. What is the maximum daily dose for neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35 kg?

   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

7. Concomitant use of domperidone with which of the following drugs is contraindicated? Check all boxes that apply.

   - ☐ Drugs that shorten the QT interval
   - ☐ Drugs that prolong the bleeding time
   - ☐ Drugs that prolong the QT interval
   - ☐ Drugs that are potent CYP3A4 inhibitors

8. In which underlying disease(s) is domperidone use contraindicated? Check all boxes that apply.

   - ☐ prolactin-releasing pituitary tumour (prolactinoma)
   - ☐ moderate to severe hepatic impairment
   - ☐ prolongation of cardiac conduction intervals, particularly QTc
   - ☐ cardiac insufficiency

- ☐ significant electrolyte disturbance
- ☐ Patients with a history of seizures
- ☐ Patients with phaeochromocytoma

9. In view of the revised label, would you prescribe domperidone for any of the following? Check all boxes that apply.
   - ☐ Postural hypotension in patients with Parkinson's disease
   - ☐ Stimulation of lactation in breastfeeding women
   - ☐ Gastroparesis
   - ☐ Treatment of gastro-oesophageal reflux disease (GERD)
   - ☐ Dyspepsia
   - ☐ Inflammatory Bowel Syndrome (IBS)
   - ☐ Relief of the symptoms of nausea and vomiting

----------end of survey----------