Domperidone IND Packet

For Sponsors Treating Patients with Gastrointestinal Motility Disorders

1. Domperidone Background

Domperidone is not currently a legally marketed drug or approved for sale in the U.S. On June 7, 2004, FDA issued a warning that compounding domperidone is illegal, and issued an import alert advising FDA field personnel that they may detain shipments of finished drug products and bulk ingredients containing domperidone. This warning was the result of the Agency's concern about the potential public health risks associated with the use of domperidone by lactating women to enhance breast milk production (i.e., the risk of cardiac arrhythmias, cardiac arrest, and sudden death outweigh the potential benefit of domperidone use in this population). These risks are also of concern in other populations that may use domperidone (such as patients with gastrointestinal motility disorders). Although the original reports of cardiac arrhythmias, cardiac arrest, and sudden death were with the intravenous form of domperidone, there have also been similar reports with the oral form of domperidone. Furthermore, concomitant use of moderate or strong CYP3A4 inhibitors can lead to increased concentrations of domperidone, and thus increase the risk of cardiac arrhythmias, cardiac arrest, and sudden death. However, FDA recognized that there are some patients with severe gastrointestinal motility disorders that are difficult to manage with available therapy, who may benefit from domperidone and in whom its potential benefits outweigh its risks.

2. Obtaining an IND

FDA currently allows patients 12 years of age[1] and older with various gastrointestinal (GI) motility conditions to be treated with domperidone through the Expanded Access to Investigational Drugs program. These conditions include gastroesophageal reflux disease with upper GI symptoms, gastroparesis, and chronic constipation. Patients must have failed standard therapies to be eligible to receive domperidone. The Expanded Access program facilitates availability of investigational drugs (such as domperidone) to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

To help facilitate the IND process, FDA has developed this packet, which includes instructions, templates, checklists, a protocol outlining the treatment plan (multi-patient INDs only), and summary of regulatory requirements. As sponsors of an active IND, physicians can prescribe domperidone to qualifying patients.

3. Application Process

A physician may open an IND for a single patient or for multiple patients. For those physicians treating only one patient, the consolidated FDA Form 3926 can be used in lieu of the 1571 and 1572 forms. Physicians that anticipate treating more than one patient in one year are advised to submit an Intermediate Size Patient Population (multi-patient) IND. Multi-patient INDs allow for consolidated reporting and reduced administrative paperwork in the long-run.

[1] There may be situations where younger patients qualify to receive domperidone. FDA will assess these situations on a case-by-case basis.

Single Patient IND (SPI)

To open an SPI, the physician must submit an application that includes the following:

- Cover letter (see Attachment B)
- Form 3926*
- Copy of the Informed Consent document planned for use (see section 7)
- Clinical Protocol (see Attachment D)

* Download the 3926 form online before completing, printing and signing:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM504572.pdf

Be sure to include everything that boxes 4 and 5 require (clinical history and treatment information) for the patient. You may refer to our standard protocol (see Attachment D) to ensure your treatment plan is consistent with what we ask sponsors to follow for multi-patient INDs.

Intermediate Size Patient Population (multi-patient) IND

To open a multi-patient IND, the physician must submit an application that generally includes the following:

- Cover letter (see Attachment B)
- Form 1571 (see Attachment C)
- Form 1572 (see Attachment C)
- Curriculum Vitae (CV), resume or other statement of qualifications
- Clinical Protocol (see Attachment D)
- Copy of the Informed Consent document planned for use (see section 7)

Applications should be submitted to the following address via paper or preferably via electronic submission:

Paper Submissions:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology
Central Document Room
5901B Ammendale Road
Beltsville, MD 20705-1266

Electronic submissions:

You may choose to submit your IND and future information as an electronic submission via the FDA CDER NextGen Portal. You will need to request an account in order to log in and utilize the portal. For additional information, see FDA.gov[2,3].

Upon receipt of the IND by FDA, an IND number will be assigned, and the application will be forwarded to the Division of Gastroenterology and Inborn Errors Products. **It is imperative that you are available during our review of your application in the event that we have questions. Unresolved issues may lead to a clinical hold.** The reviewing division will send an acknowledgement letter to you (the Sponsor-Investigator) providing notification of the IND number assigned, contact information for the FDA Division and regulatory project manager, and reporting requirements. Normally, you cannot initiate any studies (i.e., administer the investigational drug) until 30 days after the date FDA receives the IND. However, the acknowledgement letter usually contains language notifying you that studies may begin upon receipt of the letter.

4. Regulatory Responsibilities as a Sponsor

Your ongoing responsibilities as the Sponsor-Investigator of an IND include:

- Obtaining informed consent of patients to be treated under the IND
- Monitoring patients treated under the IND
- Maintaining control of and keeping records on the drug dispensed under the IND
- Notifying FDA of any changes made to the IND (e.g., changes to the protocol, a change in drug supplier)
- Reporting to FDA serious, fatal, and/or life-threatening adverse events that are associated with use of the drug (see Attachment E)
- Submitting an annual report to the IND (see Attachment E) within 60 days of the anniversary date you are permitted to initiate studies (i.e., begin administering the investigational drug), which is usually 30 days after FDA receives the application.
- Regularly visiting the FDA Website for important updates to this packet, e.g., regarding drug interactions or protocol changes.

5. Ordering Domperidone

Domperidone is not approved for sale in the U.S. and is therefore considered an investigational drug. Investigational drugs can come from many sources including foreign and domestic pharmaceutical manufacturers. Authorization must be obtained from FDA prior to the importation, interstate shipment, and administration of domperidone. To facilitate the IND process of importing domperidone, which may otherwise be detained upon importation, FDA has identified a dispensing pharmacy (see Attachment A).

Patients can order domperidone directly from the pharmacy supplier. The patient will need to provide the pharmacy with the IND number and your name when placing the order. The pharmacy maintains a

[2] https://edm.fda.gov/

[3] https://www.fda.gov/media/128774/download

list of active IND #s. Therefore, it is imperative that you submit a copy of the Acknowledgment Letter (which authorizes you to prescribe domperidone under an active IND) that we issue to you which includes the IND #.

6. Financial Responsibility

U.S. regulations prohibit charging a patient for an investigational drug unless FDA gives authorization to do so (see 21 CFR 312.8). **A request to charge must be made if the sponsor or pharmacy plan to charge the patient or health insurance provider for the cost of the drug.** In this case, cost recovery would extend only to the cost of the drug and associated shipping costs. Commercialization of an investigational drug is prohibited.

Domperidone is provided by the pharmacy supplier directly to the patient and there **is no need for the investigator to request for charge**. In rare circumstances, the investigator/physician directly obtains domperidone from the pharmacy supplier. In this situation, investigator/physician can request to charge in the IND application by checking **Charge Request** in box # 12 of the 1571 and by checking the box next to appropriate box in the cover letter provided in this packet and must provide an explanation and amount for the charge request. The investigator/physician **must renew the request to charge annually** from the original approval date.

The FDA will respond in writing with the authorization to charge as part of the Acknowledgement letter for the IND. Note that under 21 CFR 312.8, the price charged may not be larger than necessary to recover direct costs; and that under 21 CFR 312.8, authorization to charge for an investigational drug may be withdrawn by FDA if we find that the conditions underlying the authorization are no longer satisfied.

7. Human Protection

Contacting your IRB

An Institutional Review Board (IRB) is a group formally designated by an institution to review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects. The primary purpose of IRB review is to assure that the rights and welfare of human subjects are protected, and to determine that informed consent is obtained in accordance with and to the extent required by Federal requirements.

Under the IND regulations (21 CFR 312), you must ensure that an IRB that complies with FDA regulations (21 CFR 56) will be responsible for the initial and continuing review and approval of the proposed clinical protocol. You must also assure that you will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects and that you will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

You must provide the name and address of the IRB that will be responsible for the review of your proposed clinical protocol on form FDA 1572 "Statement of Investigator." If using the form FDA 3926, the Certification statement in box #11 contains this information.

Many institutions have their own IRB to oversee human subjects research conducted within the institution or by its staff. If you do not have access to a local IRB, an independent IRB may be used. The

Department of Health & Human Services' Office for Human Research Protections maintains a database of registered IRBs. Go to http://ohrp.cit.nih.gov/search/irbsearch.aspx?styp=bsc and click on "Advanced Search." Enter your state to find registered IRBs in your area.

For questions about locating an IRB, you may email FDA's Office of Scientific Investigations at CDER-OSI-GCPReferrals@fda.hhs.gov, or contact Quynh-Van Tran at 301-796-0185.

Informed Consent Documents

Your IRB may have an Informed Consent Document that they prefer you use. When creating an Informed Consent, please consult the elements of informed consent:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25

In the content of your Informed Consent Document, you must at a minimum address the following risks in addition to ensuring that all requirements of 21 CFR 50 are met. In doing so, you must capture the key safety issues associated with the following:

1. Cardiovascular Risk
2. Drug Interactions that Increase the Risk of Serious Adverse Reactions Associated with Domperidone including Torsade de Pointes, cardiac arrest, and death.

Although the original reports of cardiac arrhythmias, cardiac arrest, and sudden death were with the intravenous form of domperidone, there have also been similar reports with the oral form of domperidone. Furthermore, concomitant use of moderate or strong CYP3A4 inhibitors can lead to increased concentrations of domperidone, and thus increase the risk of cardiac arrhythmias, cardiac arrest, and sudden death. See the list of drugs in the Protocol (Attachment D) section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone".

8. Secure Email

Secure email between FDA and sponsors is useful for informal communications when confidential information may be included in the message (e.g., confidential patient information). Parties who would like to establish secure email with FDA should email a request to SecureEmail@fda.hhs.gov.

Attachment A - Suppliers

Pharmacy Suppliers

Dougherty's Pharmacy
Contact: Nita Moore
12835 Preston Road Suite #202
Dallas, Texas 75230
Pharmacy (214) 373-5300
Doctor's Line (214) 373-5395
Fax (214) 373-5330
motilium@doughertys.com

Manufacturer

Janssen Pharmaceuticals
Domaine de Maigremont
Val-De-Reuil
27100 France

Attachment B - Cover Letter

Please edit directly to suit your needs

[Date]

Jessica Lee, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology
Central Document Room 5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

Subject: New Intermediate Size Patient Population IND Application for Domperidone
or (circle or delete one)
Subject: New Single Patient IND Application for Domperidone

Dear Dr. Lee,

I am hereby submitting an Investigational New Drug application (IND) under section 505(i) of the Federal Food, Drug, and Cosmetic Act and in accord with 21 CFR 312 for domperidone tablets.

This application contains the following (*check all that apply)*
(Refer to application process section 3 in packet to determine what needs to be included):

☐ Form 3926 (Single Patient IND only)
☐ Form 1571 (for immediate size patient population IND) and Form 1572 (include CV or resume)
☐ Copy of Informed Consent planned for use
☐ Copy of the Protocol

You must check the following box if you are requesting to charge for Domperidone
*(**In rare circumstances; see Financial Responsibility in Domperidone Packet (Section 6)**):*
☐ Permission is requested, under 21 CFR 312.8, to charge for the investigational drug used in this IND.
☐ Explanation why you are requesting to charge, and the amount requested
☐ I have included justification for the cost to be recovered or will submit documentation after purchase, which is consistent with 21 CFR 312.8 and agree not to profit

I plan to provide domperidone prescriptions to approximately _____ (#) patients under this IND.

The name and address of the supplier of the domperidone tablets to be administered under this IND is _____.

I claim a categorical exclusion from environmental assessment requirements (under 21 CFR 25.31[e]) for this IND. To my knowledge, no extraordinary circumstances exist.

Sincerely,

Attachment C – FDA 1571 and 1572 Forms

Fillable Forms FDA 1571 and 1572 and corresponding instructions can be found at:
https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm
More specific instructions are listed below (numbers correspond to numbered boxes on form):

FDA 1571

1. Insert the name of the Sponsor-Investigator (physician).
7. Indication is **to treat patients with gastrointestinal motility disorders who have failed standard therapy**
8-10 Leave blank
11. Check **Initial Investigational New Drug Application (IND)**
12. Check **Charge Request, 21 CFR 312.8** if the sponsor or pharmacy plans to charge the patient **Intermediate Size Patient Population, 21 CFR 312.315** (unless only one patient will be treated, in that case you would check Individual Patient Non-Emergency 21 CFR 312.310).
13. Contents of the Application:

    Items 2, 3, 4:

    May be briefly addressed in the cover letter or in a summary

    Item 5:

    Because domperidone is approved for use in another country, the approved professional labeling (in English) can be submitted in lieu of the Investigator's Brochure.

    Item 6a:

    See Attachment D (Protocol)

    Items 6b, 6c, 6d:

    Included in Form FDA 1572

    Items 7, 8:

    If domperidone is obtained from one of the authorized manufacturer suppliers (see Attachment A), no additional information needs to be submitted for items 7 or 8.

15-16. Note there are certain important commitments that the Sponsor-Investigator makes by signing the form FDA 1571, which are listed below box 15.
17-25. Original signature by the Sponsor-Investigator

FDA 1572

Form FDA 1572 with its attachments may satisfy Form FDA 1571, box 12, items 6 b-d. Information can be supplied in the form of attachments (such as a curriculum vitae) rather than entering that information directly onto the form, but this should be so noted under the relevant section numbers.

3-4. Name and address of facility where the clinical investigation(s) will be conducted and any clinical laboratory to be used
5. Insert the name and address of your Institutional Review Board (IRB) (see section 7)
6. List any residents, fellows, research nurses, or others assisting the physician
7-8. N/A

Attachment D - Domperidone Protocol

Please use track-changes if you deviate in any way from this protocol

Domperidone is a dopamine antagonist with gastroprokinetic properties; domperidone does not readily cross the blood-brain barrier.

Purpose:

To provide oral domperidone to patients ≥12 years of age where, according to the investigator's judgment, a prokinetic effect is needed for the relief of refractory gastroesophageal reflux disease (GERD) with upper gastrointestinal (GI) symptoms, gastroparesis, and chronic constipation in patients whom the potential benefit may outweigh the risk of cardiovascular adverse reactions including QT prolongation, Torsades de Pointes, and death.

Objective:

To allow the use of domperidone by patients with gastrointestinal motility disorders who have failed standard therapy.

Inclusion Criteria:

1. Male or female
2. Age 12 and older
3. Symptoms or manifestations secondary to gastrointestinal motility disorders, including GERD (e.g., persistent esophagitis, severe dyspepsia, heartburn), gastroparesis (e.g., nausea, vomiting, early satiety, abdominal pain, postprandial fullness), or severe chronic constipation, that are refractory to standard therapy.
4. Patients must have a comprehensive evaluation to eliminate other causes of their symptoms.
5. Patient has signed informed consent for the administration of domperidone that informs the patient of potential adverse events including:
    - cardiac arrhythmias including QT prolongation and death
    - increased prolactin levels
    - extrapyramidal side effects
    - breast changes
    - There is a potential for increased risk of adverse events with the drugs listed on page 14.

Exclusion Criteria:

History of, or current, arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes. Patients with minor forms of ectopy (PACs) are not necessarily excluded.

1. Clinically significant bradycardia, sinus node dysfunction, or heart block. Prolonged QTc (QTc > 450 milliseconds for males, QTc>470 milliseconds for females).
2. Hepatic dysfunction
3. Renal insufficiency, defined as estimated GFR < 90 ml/min/1.73m^2
4. Clinically significant electrolyte disorders.
5. Gastrointestinal hemorrhage or obstruction
6. Presence of a prolactinoma (prolactin-releasing pituitary tumor).
7. Pregnant or breast feeding female
8. Known allergy to domperidone

Treatment Plan:

Oral domperidone 10-30 mg administered QID. Patients should be started at the lowest dose and maintained at the lowest effective dose given the increased risk of serious cardiovascular reactions with increasing exposures of domperidone. Patients should be evaluated before doses are increased (see the Assessment and Monitoring Requirements for Domperidone INDs table below).

Withdrawal Criteria:

1. Patients may withdraw from the trial at any time.
2. Patients must be withdrawn for the following:
   a. The patient withdraws consent.
   b. While on treatment, EKGs demonstrate QTc> 450 milliseconds for males, QTc>470 milliseconds for females, or there is a change in QTc greater than or equal to 60 milliseconds from baseline.
   c. Development of serious electrolyte abnormalities.
   d. The patient is not receiving therapeutic benefit from domperidone.

(Please note that the reason for withdrawal must be reported)

Assessment and Monitoring Requirements for Domperidone INDs:

	Screening Visit	Every 2-Month Visit[1] (the first year)	Every 6-Month Visit[1] Thereafter
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Medical History	X	X	X
Physical Exam	X	X	X
12-Lead EKG	**See footnote #2: EKG Monitoring**		
Assessment of labs (CBC, liver panel, renal panel)	X[3]	X	X
Vital signs	X	X	X
(Re)Assessment of domperidone use (Benefit/Risk)		X	X
Review concomitant medication	X	X	X
Adverse events		X	X

1. **Required Additional Visits:**
   - ***If an increase in domperidone dose is being considered***, schedule an ***additional patient visit*** to perform each of the evaluations shown ***prior to increasing the domperidone dose***. In all patients whose domperidone dose was increased, perform each of the evaluations shown at an ***every 2-month visit for the first year after the domperidone dose was increased***, and then at an ***every 6-month visit thereafter***.

- ***If considering starting any concomitant medication that may interact with domperidone***, schedule an ***additional patient visit*** to perform each of the evaluations shown ***prior to starting the concomitant medication*** (see list below in the section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone"). In all patients who have started any concomitant medication that may interact with domperidone, perform each of the evaluations shown at an ***every 2-month visit for the first year after the concomitant medication was started***, and then at an ***every 6-month visit thereafter***.

2. **EKG Monitoring:**
   - Screening Visit:
     - A ***new 12-Lead EKG*** will be obtained at the Screening Visit.
   - Assessment Immediately After Initiation of Domperidone:
     - ***In all patients***, a 12-Lead EKG will be obtained ***3 to 7 days after domperidone is started.***
     - Timing of the EKG will be ***1 hour after the first domperidone dose of the day*** in which the EKG is done.
     - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
   - Routine EKG Monitoring on a Stable Dose of Domperidone:
     - ***In all patients***, obtain an EKG at an ***every 2-month visit for the first year***, and then at an ***every 6-month visit thereafter***.
     - Timing of the EKG will be ***1 hour after the first domperidone dose of the day*** in which the EKG is done.
     - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
   - Additional EKG Requirements if a Domperidone Dose Increase is Being Considered:
     - ***In all patients***, a 12-Lead EKG will be obtained ***at the additional visit prior to increasing the domperidone dose***, and ***3 to 7 days after the domperidone dose is increased***.
     - Timing of the EKG will be ***1 hour after the first domperidone dose of the day*** in which the EKG is done.
     - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
     - ***In all patients whose domperidone dose was increased***, obtain an EKG at an ***every 2-month visit for the first year after the domperidone dose was increased***, and then at an ***every 6-month visit thereafter***.
   - Additional EKG Requirements if Starting Any Concomitant Medication that May Interact With Domperidone:
     - ***In all patients,*** a 12-Lead EKG will be obtained ***prior to starting the concomitant medication*** and ***3 to 7 days after the concomitant medication is started*** (see list below in the section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone").
     - Timing of the EKG will be ***1 hour after the first domperidone or domperidone/concomitant medication dose of the day*** in which the EKG is done.
     - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
     - ***In all patients who have started concomitant medications*** (see list below in the section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone"), obtain an EKG at

an ***every 2-month visit for the first year after the concomitant medication was started***, and then at an ***every 6-month visit thereafter***.

3. **Assessment of Labs**:
   - Screening Visit:
     - For the initial screening, ***lab values from the prior 3 months*** may be assessed.

Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone.

The following drugs are moderate and strong inhibitors of CYP3A4, and may increase the drug levels of domperidone. There is an increasing risk of clinically significant QT prolongation, Torsade de Pointes, and death with increasing levels of systemic domperidone:

1. Antidepressants: doxepin (Adapin®, Sinequan®, Zonalon®), clomipramire (Anafril®), amoxapine (Asendin®), trazodone (Desyrel®), venlafaxine (Effexor®), nefazodone (Serzone®), fluvoxamine (Luvox®), paroxetine (Paxil®), fluoxetine (Prozac®, Saerfem®), sertraline (Zoloft®), amitriptyline (Elavil®, Endep®, Etrafon®, Limbitrol®, Triavil®), maprotiline (Ludiomil®), desipramine (Norpramin®), nortriptyline (Pamelor®), trimipramine (Surmontil®), imipramine (Tofranil®), protriptyline (Vivactil®),
2. Anti-psychotics: haloperidol (Haldol®), chlorpromazine (Thorazine®, Ormazine®), chlorpromazine pimozide (Orap®), sertindole (Serlect®), quetiapine (Seroquel®), mesoridazine (Serentil®), perphenazine (Triavil®), lfluphenazine (Apo-Fluphenazine®, Modecate Concentrate®, Moditen®, Permitil®, PMS-Fluphenazine®, Prolixin®, Rho-Fluphenazine®), promazine (Sparine®), trifluoperazine (Stelazine®)
3. Anti-Emetics: prochlorperazine (Compazine®), thioridazine (Mellaril®), promethazine (Phenergan®), mesoridazine (Serentil®), thiethylperazine, (Torecan®), perphazine (Trilafon®), dolasetron (Anzemet®), dronabinol (Marinol®), droperidol (Inapsine®)
4. Anti-infective agents: erythromycin (such as E.E.S.®, E-Mycin®, Ilotycin® , Pediazole®, Aknemycin®), clarithromycin (Biaxin®), troleandomycin (TAO®), norfloxacin (Chibroxin®, Noroxin®), quinine sulfate, quinupristin and dalfopristin (Synercid®), pentamidine (Nebupent®, Pentacarinat®, Pentam®), sparfloxacin (Zagam®), grepafloxacin (Raxar®), azithromycin (Zithromax®), ofloxacin (Floxin®). Levofloxacin (Levaquin®)
5. Anti-Fungal Agents: fluconazole (Diflucan®), itraconazole (Sporanox®), ketoconazole (Nizoral®), miconazole (Micatin®, Monistat®), terconazole (Terazol®), ticonazole (Vagistat®), butaconazole (Femstat 3®), posaconazole (Noxafil®)
6. Antivirals: foscarnet (Foscavir®)
7. Protease Inhibitors: indinavir (Crixivan®), amprenavir (Agenerase®), ritonavir (Norvir®), nelfinavir (Viracept®), saquinavir (Invirase®, Fortovase®),
8. Anti-Hypertensives: nicardipine (Cardene®), isradipine (Dynacrirc®), moexipril/ HCTZ (Uniretic®)
9. Calcium Channel Blockers: verapamil (Calan®), diltiazam (Cardizem®), diltiazem/enalapril (Teczem®), verapamil/trandolapril (Tarka®), tocainide (Tonocard®), bepridil (Vascor®)
10. Anti-Arrhythmics: disopyramide (Norpace®, Norpace CR®), quinidine (such as Quinidex®, Cardioquin®, Quinaglute®, Duraquin®), procainamide (Procanbid® , Procan®, Pronestyl®,), flecainide (Tambocor®), sotalol (Betapace®), bretylium (Bretylol®), amiodarone (Cordarone®), ibutilide (Corvert®), moricizine (Ethmozine®)
11. Diueretics: bumetanide (Bumex®), furosemide (Lasix®), torsemide (Demadex®), etharcrynic Acid (Edecrin®), chlorothiazide (Diuril®), Indapamide (Lozol®)
12. Antilipemics: Bepridil (Vascor®), mibefradil (Posicor®),
13. Hematological Agents: cilostazol (Pletal®)
14. Respiratory Agents: zafirlukast (Accolate®), salmetrol (Serevent®)
15. Gastrointestinal Agents: cimetidine (Tagamet®), cisapride (Propulsid®)
16. Antidiarrheal: octreotide (Sandostain®)
17. Antihistamines: azelastine (Astelin®), clemastine (Tavist®)
18. Migraine treatment: naratriptan (Amerge®), sumatriptan (Imitrex®), zolmitriptan (Zomig®)
19. Antimalarial: halofantrine

20. Muscle relaxants: tizanidine (Zanaflex®)
21. Miscellaneous: tamoxifen (Nolvadex®), warfarin (Coumadin®), phenytoin (Dilantin®), ziprasidone (Geodon®), risperidone (Risperdal®), formoterol fumarate (Foradil Aerolizer®), sildenafil (Viagra®)

Attachment E - Adverse Event and Annual Reporting

Adverse Event Reporting

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act, and the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. Your responsibilities include the following.

- Communicating any unexpected fatal or immediately life-threatening reactions associated with use of this product, either by email Richard.Whitehead@fda.hhs.gov or fax (301-837-6424) no later than 7 calendar days after initial receipt of the information.
- Submitting all serious, unexpected adverse experiences as well as results from animal studies that suggest significant clinical risk within 15 calendar days after initial receipt of this information [21 CFR 312.32]. You may submit your safety report using FDA Form 3500 or in narrative format with the title "IND Safety Report".

Definitions

"Associated with the use of the drug"- There is a reasonable possibility that the experience may have been caused by the drug.
"Disability" - A substantial disruption of a person's ability to conduct normal life functions.
"Life-threatening adverse drug experience"- Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred.
"Serious adverse drug experience"- Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
"Unexpected adverse drug experience"- Any adverse drug experience, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Annual Reporting

As sponsor of this IND, you are responsible for submitting written progress reports, which are required at intervals not exceeding one year and are due within 60 days of the application anniversary date (i.e., the date you were allowed to proceed with treatment under your IND number). Please include:

- A brief summary of the status of each patient enrolled in the protocol as it relates to their use of domperidone. If there is more than one protocol, identify the protocol.
- The total number of subjects you plan to treat under the protocol; the number entered into treatment to date, and the number who dropped out of the study for any reason.
- A description of the general investigational plan for the coming year.

A draft letter is provided for your convenience:

Date IND #

Annual Report

Jessica Lee, M.D.,
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology
Central Document Room
5901B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Lee,

In compliance with 21 CFR 312.33, I am submitting an annual report to IND (please provide IND number) for domperidone submitted on (provide date the IND was submitted to FDA).

This annual report covers the time period from (for the first annual report, state the date you were permitted by FDA to administer domperidone) to (the ending date of your summary of treatment).

Title of protocol:
Status of each patient studied:
Number of patients planned for enrollment:
Number of patients enrolled to date:
Number of patients who dropped out:
General investigational plan for coming year:

If you have any questions, you may reach me at (provide phone number and email).

Sincerely,