DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Schwarz Pharma, Inc.

Dear :

To obtain needed pediatric information on *metoclopramide* for the treatment of the signs and symptoms of *gastroesophageal reflux disease*, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies. Please note that since the efficacy and safety of *metoclopramide* in *gastroesophageal reflux disease* has not been established by adequate and well controlled trials in pediatric patients, in addition to bridging to adult pharmacokinetic (PK) data, an indication for *gastroesophageal reflux disease* would require replicated evidence of efficacy in the pediatric population.

Introduction: Gastroesophageal reflux (GER) is defined as the retrograde passage of gastric contents into the esophagus. Gastroesophageal Reflux Disease (GERD) is defined as GER with associated symptoms such as vomiting, poor weight gain, dysphagia, abdominal or substernal pain, heartburn, and/or respiratory disorders.

Tools used to diagnose GERD include the medical history, physical examination, pH probe and esophageal endoscopy (with or without biopsy). Prolonged gastroesophageal pH monitoring is currently the most objective and widely used test for the detection of pathologic GERD in pediatric patients.

Once a pediatric patient is diagnosed with GERD, the options for treatment are similar to the options for adult patients. Whereas certain dietary factors may exacerbate GERD symptoms, little data suggest a causative role for diet in the pathogenesis of reflux events. Nonetheless, the first step is to make changes to diet, and positioning followed by pharmacologic intervention, and rarely, surgery.

The pharmacologic options include acid buffering therapies (antacids), prokinetics, drugs that coat esophageal erosions and ulcers (sucralfate) and drugs that suppress gastric acid production (H2RA, PPI). While use of these drugs is common in pediatric practice, they are not all labeled for use on the pediatric population. Propulsid® (cisapride), a prokinetic drug approved for the treatment of GERD in adults, was approved for use in 1993. Although never approved for use in

the pediatric population, it was available as a suspension. There were many reports of serious adverse cardiac events, including deaths in infants. The labeling was strengthened to communicate this potential risk. Jannsen Pharmaceuticals ultimately stopped marketing cisapride in 2000. Cisapride is now available only through a Limited Access Program, which includes pediatric patients.

Much of the off-label use of metoclopramide occurs in the neonatal period where there is extensive concern about GERD and apnea and bradycardia. While this practice is common, there is little evidence that apnea is related to GERD in premature infants. Because of safety concerns associated with this medication, namely, neurological adverse events that are more frequently seen in younger than in older patients, studies should first be performed in older patients, with sequential enrollment down to younger patients if safety and efficacy are established in these older age groups. Studies of the safety and efficacy in the neonatal age group (defined as the first 28 days following birth) may be requested in the future if safety is established in the older pediatric population, and if studies can be designed to identify and measure clinically significant endpoints of GERD in this population.

Scientific Questions to be Answered

1. What is the PK/PD profile of metoclopramide in pediatric patients, ages 1 to 16 years?
2. Is metoclopramide safe and effective when used to treat gastroesophageal reflux in pediatric patients, ages 1 to 16 years?

Preliminary Study

Type of Study: This will be a nonclinical study. Prior to conducting clinical Studies 1 and 2, the sponsor must conduct "*in vitro metabolism and drug interaction*" studies (See Agency Guidance entitled: Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro, 1997 or its current version). These studies are needed to understand the metabolic pathways involved in metoclopramide metabolism in pediatric patients and identify the enzyme systems that metoclopramide may inhibit and/or induce. This information can highlight potential drug-drug interactions between metoclopramide and likely to be co-administered drugs, and ultimately lead to appropriate use and labeling in pediatric patients. The study reports including raw data and methodology of the *in vitro* metabolism and drug interaction studies must be submitted to the Agency prior to initiating any clinical studies. An appropriate genotyping platform should be used to genotype pediatric patients for CYP2D6 and other enzyme systems, based on the findings of the *in vitro* metabolism and drug interaction studies.

This nonclinical study must be submitted to and reviewed by the Agency prior to initiating Studies 1 and 2. In the event that a drug-drug interaction is identified, the relevant finding (s) of the preliminary study will be incorporated into Studies 1 and 2.

Study 1:

Type of Study: This will be a repeated dose PK, PD, and safety study of at least three dose-levels of oral metoclopramide at steady state.

Objective/rationale: To evaluate the multi-dose pharmacokinetics, pharmacodynamics, and safety of metoclopramide in pediatric patients, ages 1 year to 16 years, with GERD.

Indication to be studied: Treatment of pediatric patients diagnosed with GERD.

Inclusion Criteria: Pediatric patients with GERD. The sponsor must specify and justify the methodology to diagnose GERD. Patients with neurologic impairment without active seizures and with GERD may be included in the study.

Exclusion Criteria: At a minimum, patients with a known history or a family history of neuroleptic malignant syndrome, seizure disorder, pheochromocytoma, porphyria, aldosterone abnormalities, eosinophilic and erosive esophagitis, disorders that may predispose the patient to methemoglobinemia, GERD secondary to other illnesses and patients receiving other drugs that are likely to cause extrapyramidal reactions must be excluded.

Study Design: This will be an open label, randomized 1:1:1, repeat dose PK, PD, and safety study at steady state of at least three dose-levels of metoclopramide in pediatric patients, ages 1 year to 16 years. Adequate justification for dose selection must be provided.

The study will be designed to characterize the change in intraesophageal pH after repeated doses of metoclopramide at steady state. At least 18 patients in the age group 1 to < 6 years (at least 6 patients per dosage group) and at least 12 patients in each of the age groups 6 to <12 years and 12 to 16 years (at least 4 patients per dosage group) must complete pharmacokinetic assessments if a standard PK approach is used. Alternatively, a population PK approach may be used with patients approximately evenly distributed across the age and treatment groups. Pharmacodynamic assessments of intraesophageal pH will be performed in at least six patients in each dosage group who require tube placement or pH monitoring for clinical management not related to the protocol and in whom such measurements would be appropriate.

Studies should be performed in older pediatric patients first, with sequential enrollment down to younger patients, provided safety is established in the older age groups.

All concomitant medications must be documented.

Age group and population in which study will be performed: Pediatric patients of both genders from 1 to 16 years of age will be enrolled. These patients will be distributed approximately equally between the following age groups with even distribution across each age range:

- 1 to <6 years
- 6 to < 12 years
- 12 to 16 years

Number of patients to be studied or power of study to be achieved: At least 18 patients in age group 1 to < 6 years (at least 6 in each dosage group) and at least 12 patients in each of the other age groups, 6 to 12 years and 12 to 16 years (at least 4 in each dosage group) will complete pharmacokinetic assessments if a standard PK approach is used. Alternatively, a population PK approach may be used in which the protocol will specify and justify the number of patients to be studied and samples to be taken in order to complete the pharmacokinetic assessments needed.

Endpoints:

Pharmacokinetics: For both the single- and repeated-dose portions of the studies, AUC, apparent total clearance, T_{max}, $T_{1/2}$, apparent volume of distribution, C_{max}, and other pharmacokinetic parameters, as appropriate.

Pharmacodynamics: In the PD studies, 24 hour intra-esophageal pH monitoring will be performed.

Appropriate pharmacodynamic parameters will be assessed. The primary pharmacodynamic endpoint will be the percent time intra-esophageal pH $\geq$4. As secondary endpoints, measures of gastric emptying (e.g., esophageal intraluminal impedance) may be assessed.

Safety and tolerability: In this study, the evaluation of safety must include, at a minimum, a physical examination and clinical laboratory assessment before treatment and after completion of the pharmacokinetic, pharmacodynamic and clinical outcome assessments. Clinical outcome assessments should include weight gain and improvement in other symptoms of GERD, as well as assessment of nutritional parameters such as, but not limited to, body mass index, albumin and pre-albumin levels.

All patients must be monitored for extrapyramidal symptoms (e.g., dystonic reactions), tardive dyskinesia, neuroleptic malignant syndrome and cardiac adverse events (see **Drug Specific Safety Concerns**).

Assessments of adverse events will occur throughout each patient's study participation. Patients will be followed until adverse events have been adequately resolved. Withdrawals from the studies because of serious adverse events or treatment failure must be documented, as will the use of any rescue medications. All patients will be followed at least 2 weeks after final administration of test medication. Patients enrolled in Study 1 will undergo follow-up developmental, growth, and safety assessments 6 and 12 months after enrollment.

Study Evaluation:

Pharmacokinetics: In the PK studies, appropriate pharmacokinetic parameters will be assessed for the repeated-dose, steady state study (e.g., AUC, apparent total clearance, T_{max}, $T_{1/2}$, apparent volume of distribution, C_{max}, and others as appropriate).

Pharmacodynamics: Pharmacodynamic assessments will be made at baseline (i.e., just prior to dosing), at appropriate intervals after dosing and after the final metoclopramide dose to encompass the duration of drug effect.

Statistical information (statistical analyses of the data to be performed): In the pharmacokinetic study, the pharmacokinetic parameters for metoclopramide may be summarized using descriptive statistics. In the pharmacodynamic study, the pharmacodynamic analysis should include an assessment of the time course of change of intra-esophageal pH, along with an assessment of dose effects.

The correlation between pharmacokinetic and pharmacodynamic parameters and safety should be assessed.

Study 2:

PK/PD data as well as the correlation between pharmacokinetic and pharmacodynamic parameters and safety data obtained in Study 1 should be submitted and reviewed by FDA and the drug should be determined to be safe before proceeding to Study 2. In addition, the information derived from Study 1 will guide the choice of dosing for Study 2.

Type of study: Multi-center, randomized, double-blind, safety and efficacy study of metoclopramide for the treatment of GERD in pediatric patients, ages 1 year to 16 years of age. The study design may be placebo- OR active-controlled. If active-controlled, metoclopramide may be add-on therapy to the active control. The rationale for the choice of study design must be specified and justified in the protocol. If active-controlled, the study may be powered to demonstrate superiority OR non-inferiority of metoclopramide to the active comparator. The rationale for the choice of superiority or non-inferiority must be specified in the protocol. If metoclopramide is administered as add-on therapy to active therapy, the combination of metoclopramide plus active therapy would need to be superior to active therapy alone.

Objective/rationale: Evaluate the safety and efficacy of metoclopramide in the treatment of pediatric patients with GERD.

Indication to be studied: Treatment of pediatric patients diagnosed with GERD.

Inclusion Criteria: Pediatric patients with GERD. The sponsor must specify and justify the methodology to diagnose GERD. Patients with neurologic impairment without active seizures and with GERD may be included in the study.

Exclusion Criteria: At a minimum, patients with a known history or a family history of neuroleptic malignant syndrome, seizure disorder, pheochromocytoma, porphyria, aldosterone abnormalities, disorders that may predispose the patient to methemoglobinemia, patients with GERD secondary to other illnesses, patients with eosinophilic esophagitis, and patients receiving other drugs that are likely to cause extrapyramidal reactions must be excluded.

Patients with erosive esophagitis will be excluded from the study. However, if a placebo-controlled trial design is used, consideration will be given to allow pediatric patients with erosive esophagitis to participate in the trial if they are receiving adequate therapy to treat the esophagitis.

Study Design: Multi-center, randomized, placebo- OR active-controlled, double-blind, safety and efficacy study of oral metoclopramide for the treatment of GERD in pediatric patients ages 1 to 16 years of age.

To be included in this study, patients will:
(a) be 1 to 16 years of age inclusive,
(b) have GERD, and
(c) have had endoscopic examination as part of their diagnostic evaluation.

The duration of study treatment will be 12 weeks.

All concomitant medications must be documented.

Age group and population in which study will be performed:
Pediatric patients of both genders, ages 1 through 16 years, will be enrolled. These patients will be distributed approximately equally between the following age groups with even distribution across each age range:

- 1 to <6 years
- 6 to < 12 years
- 12 to 16 years

Number of patients to be studied or power of study to be achieved:
The study must be powered to show that metoclopramide is superior to placebo OR that metoclopramide is superior to or not inferior to an active comparator (labeled for pediatric patients, aged 1 to 16 years, and used as directed in current labeling). If metoclopramide is added to active therapy, the combination should be superior to active therapy alone (See Statistical Information).

Regarding the PK and PD assessments, at least 18 patients in age group 1 to < 6 years (at least 6 in each dosage group) and at least 12 patients in each of the other age groups, 6 to 12 years and 12 to 16 years (at least 4 in each dosage group) will complete pharmacokinetic assessments if a standard PK approach is used. Alternatively, a population PK approach may be used in which the protocol will specify and justify the number of patients to be studied and samples to be taken in order to complete the pharmacokinetic assessments needed.

Pharmacodynamic and Clinical Endpoints:
Clinical endpoints may include improvement in signs and symptoms of pediatric GERD (e.g., vomiting, poor weight gain, dysphagia, abdominal or substernal pain, heartburn, and/or respiratory disorders), GERD symptom scores, concomitant antacid consumption, physical well-being and, in patients with erosive esophagitis who undergo follow-up endoscopy, healing of mucosal lesions. Additional clinical endpoints may be improvement in nutritional parameters such as, but not limited to, body mass index, albumin and pre-albumin levels. The protocol should specify and justify the choice of efficacy endpoints. The methodology chosen to measure efficacy must be validated in the
pediatric population.

Appropriate pharmacodynamic parameters will be assessed. The primary pharmacodynamic endpoint will be the percent time intra-esophageal pH $\geq$4. As secondary endpoints, measures of gastric emptying (e.g., esophageal intraluminal impedance) may be assessed.

Study Evaluation: Outcome measures will be assessed at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire, daily symptom diary) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes.

Signs and symptoms of pediatric GERD (e.g., vomiting, poor weight gain, dysphagia, abdominal or substernal pain, heartburn, and/or respiratory disorders) must be documented and improvement of these clinical symptoms will be assessed as proposed in the protocol. Concomitant antacid consumption and physical well-being will also be assessed as proposed in

the protocol.

Healing of mucosal lesions in patients with erosive esophagitis who undergo follow-up endoscopy must be assessed as proposed in the protocol.

In the PD studies, 24 hour intra-esophageal pH monitoring will be performed. The percentage of time spent with esophageal pH ≥4 as measured in 24 hours from baseline to end-of-study will be determined and a comparison made to the control arm. Also, the proportion of patients with a reflux index (i.e., the percentage of time that the esophageal pH is <4) greater than 6% will be compared between baseline and end-of-study and to the control arm.

If a placebo-controlled study design is used, patients who are diagnosed with erosive esophagitis must be re-scoped to document the status of the erosions. These patients will also be receiving appropriate therapy for the erosive esophagitis and metoclopramide or placebo will be "add-on" therapies.

In this study, the evaluation of safety must include, at a minimum, a physical examination and clinical laboratory assessment before treatment and at the completion of study treatment.

All patients must be monitored for extrapyramidal symptoms (e.g., dystonic reactions), tardive dyskinesia, neuroleptic malignant syndrome and cardiac adverse events (see **Drug Specific Safety Concerns**, page 8).

Assessments of adverse events must occur throughout each patient's study participation. Patients will be followed until the adverse events have been adequately resolved. Withdrawals from the studies because of serious adverse events or treatment failure will be documented, as will the use of any rescue medications. All adverse events will be followed until resolution. All patients will be followed for at least 2 weeks after final administration of test medication.

All patients enrolled in Study 2 will undergo follow-up developmental, growth, and safety assessments 6 and 12 months after enrollment.

Data Monitoring Committee: A Data Monitoring Committee (DMC) with pertinent expertise should be used to provide ongoing oversight of trial data regarding the continuing safety of subjects as well as the continuing validity and scientific merit of the trials. The charter of the committee should include guidelines for monitoring the patients. The operating plan for the DMC should be submitted to the Division for review and comment.

Statistical information: This trial must have a detailed statistical plan. Efficacy should be assessed separately for each of the three age groups to be studied (i.e., 1 to <6 years, 6 to <12 years and 12 to <16 years).

If the study is placebo-controlled, the trial should be designed with at least 80% statistical power to detect a clinically meaningful treatment effect at conventional statistical significance (alpha= 0.05, 2-tailed).

If the study is active-controlled, the margins will be established based on the clinical endpoints that will be chosen.

Drug Specific Safety Concerns: Similar to the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions. Therefore monitoring for extrapyramidal symptoms will be required. Although rare, there have been literature reports of sudden death, cardiac arrest and *torsades de pointes* and other arrhythmias (tachycardia and SVT) induced by high doses of metoclopramide. Therefore, monitoring for cardiac adverse events will also be required.

Patients with G6PD deficiency who develop methemoglobinemia, are at increased risk for fatal hemolytic anemia if treated with methylene blue.

Drug Information:

- **Dose:** The dose used for Study 2 will be determined by the data obtained from Study 1. The maximum dose to be used will be an adult dose of 10 mg three or four times per day. Otherwise the assigned dose in mg per kilogram will be used.
- **Route of administration:** Oral
- **Formulation:** Use an age-appropriate formulation in the study (ies) described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Labeling that may result from the Studies:

Appropriate sections of the label may be revised to incorporate descriptions of the conducted studies along with clinical efficacy, safety, and pharmacokinetic data results.

Format of reports to be submitted:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation are required. Pharmacokinetic study reports must include analytical method and assay validation, individual drug concentration-time data, and individual pharmacokinetic and pharmacodynamic parameters.

In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study (ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the studies
Reports of the above studies must be submitted to the Agency on or before June 30, 2008. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED IN RESPONSE TO WRITTEN REQUEST**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – COMPLETE RESPONSE TO WRITTEN REQUEST"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request

and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, approvable, not approvable); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by section 113 of the Food and Drug Administration Modernization Act of 1997 and section 15 of the Best Pharmaceuticals for Children Act of 2002, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call , Project Manager, at .

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Beitz

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