DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-854
NDA 21-793
NDA 17-862

[inside address]

Dear :

Please refer to your new drug application NDA xx-xxx for Reglan (metoclopramide) Tablets/ Orally Disintegrating Tablets (ODT)/ Injection, which was approved on (date).

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to provide FDA with new authorities to require holders of approved drugs to develop and comply with Risk Evaluation and Mitigation Strategies (REMS) (section 505-1 of the FDCA) and make safety related labeling changes (section 505(o)(4) of the FDCA) based upon new safety information that becomes available after approval of the drug. This provision took effect on March 25, 2008.

Reglan (metoclopramide) Tablets/ ODT/ Injection were approved on (date). Current product labeling warns of the risk of tardive dyskinesia, a serious movement disorder, with chronic metoclopramide treatment. Tardive dyskinesia is often irreversible. Several risk factors, including female gender, advanced age, treatment duration and total cumulative dose have been described. Recently published analyses suggest that metoclopramide has surpassed haloperidol as the most common cause of drug-induced movement disorders.[1,2] A published FDA analysis of metoclopramide utilization patterns showed that prescription claims for cumulative periods longer than 90 days were recorded for a substantial portion of patients in that study.[3] In addition, we have become aware of continued spontaneous reports to the FDA of tardive dyskinesia associated with metoclopramide use. Exposure greater than 12 weeks was evident in a majority of these reports. This information was not available when Reglan (metoclopramide) Tablets/ ODT/ Injection Orally Disintegrating Tablets were granted marketing authorization. We consider this information to be "new safety information" as defined in FDAAA.

After consideration of the new safety information described above, we believe that safety related changes should be included in the labeling for the metoclopramide class of products, including Reglan (metoclopramide) Tablets/ ODT/ Injection. We have also determined that

[1] Kenney C, Hunter C, Davidson A, Jankovic J. Metoclopramide, an increasingly recognized cause of tardive dyskinesia. J Clin Pharmacol 2008; 48:379-384.

[2] Pasricha PJ, Pehlivanov N, Sugumar A, and Jankovic J. Drug Insight: from disturbed motility to disordered movement – a review of the clinical benefits and medicolegal risks of metoclopramide. Nat Clin Pract Gastroenterol Hepatol 2006 Mar; 3(3):138-48.

[3] Kaplan S, Staffa JA, Dal Pan GJ. Duration of therapy with metoclopramide: a prescription claims data study. Pharmacoepi Drug Saf 2007; 16: 878-881.

a REMS for each drug is necessary to ensure that the benefits of the drugs outweigh the risks. These requirements are described further below.

SAFETY LABELING CHANGES

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for Reglan (metoclopramide) Tablets/ ODT/ Injection as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~):

- The addition of a **Boxed Warning** to alert physicians of the risk of tardive dyskinesia with chronic use of metoclopramide, to include the following language:

WARNING: TARDIVE DYSKINESIA

Chronic treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with the duration of treatment and the total cumulative dose. The elderly, especially elderly women, are most likely to develop this condition.

Metoclopramide therapy should routinely be discontinued in patients who develop signs or symptoms of tardive dyskinesia. There is no known treatment for tardive dyskinesia; however, in some patients symptoms may lessen or resolve after metoclopramide treatment is stopped.

Prolonged treatment (greater than12 weeks) with metoclopramide should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia. *See **WARNINGS***

- Revisions to the **Warnings** section of the label to include the following language as the first subsection:

~~**Tardive Dyskinesia**~~
~~Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.~~

~~Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.~~

~~There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.~~

Tardive dyskinesia

Tardive dyskinesia (TD), a potentially irreversible and disfiguring disorder characterized by involuntary movements of the face, tongue, or extremities, can develop in patients treated with metoclopramide. Although the risk of tardive dyskinesia (TD) with metoclopramide has not been extensively studied, one published study reported a TD prevalence of 20% among patients treated for at least 3 months.

The prevalence of the syndrome appears to be highest among the elderly, especially elderly women. It is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

There is no known effective treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore, metoclopramide should not be used for the symptomatic control of tardive dyskinesia.

- The addition of a **Medication Guide**

In addition to the changes described above to the labeling, you should submit a proposed Medication Guide for Reglan (metoclopramide) Tablets/ ODT/ Injection. Your Medication Guide must include information about the serious risk of tardive dyskinesia and will be considered part of the proposed REMS.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement proposing changes to the approved labeling for Reglan (metoclopramide) Tablets/ ODT/ Injection in accordance with the above direction, or notify FDA that you do not believe a labeling change in warranted, and submit a statement detailing the reasons why such a change is not warranted.

Use the following designators to prominently label all submissions, including supplements, relating to this safety label change as appropriate:

Safety Labeling Changes under 505(o)(4)

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1(a) of the FDCA, we have determined that a REMS is necessary for Reglan (metoclopramide) Tablets/ ODT/ Injection to ensure that the benefits of the drugs outweigh the risks based on the new safety information described above.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. The approved Medication Guide submitted as a safety labeling change, noted above, will be considered part of the REMS in accordance with 505-1(a). Pursuant to 21 CFR Part 208 and 505-1(e)(2), FDA has determined that Reglan (metoclopramide) Tablets/ ODT/ Injection pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe use of Reglan (metoclopramide) Tablets/ ODT/ Injection. FDA has determined that Reglan (metoclopramide) Tablets/ ODT/ Injection have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Reglan (metoclopramide) Tablets/ ODT/ Injection. FDA has determined that Reglan (metoclopramide) Tablets/ ODT/ Injection are products for which patient labeling could help prevent serious adverse events. Under 21 CFR 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Reglan (metoclopramide) Tablets/ ODT/ Injection.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments of the REMS that shall be no less frequent than by 18 months, 3 years, and in the 7th year after REMS is approved. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the assessment interval.

In accordance with section 505-1, within 30 days of the date of this letter, you must submit a proposed REMS. The REMS, once approved, will create enforceable obligations.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Reglan (metoclopramide) Tablets/ ODT/ Injection. Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of Reglan (metoclopramide) Tablets/ ODT/ Injection
b. A report on periodic assessments of the distribution and dispending of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

If you do not submit electronically, please send 5 copies of your proposed REMS and REMS Supporting Document as an amendment to the NDAs. Prominently identify the amendment containing the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 17-854, 21-793 or 17-862
PROPOSED REMS

On the first page of subsequent submissions related to your proposed REMS, prominently identify the submission by including this wording in bold, capital letters at the top of the page:

SUPPLEMENT <<insert assigned #>>
PROPOSED REMS-AMENDMENT

If you have any questions, call (name), Regulatory Health Project Manager, at xxx-xxx-xxxx.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: REMS Template

Appendix A- REMS Template

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B), (C), and (D), listed above.

E. Timetable for Submission of Assessments

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.

Appendix B - REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background

2. Goals

3. Supporting Information on Proposed REMS Elements

    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Assessment of the REMS

4. Information Needed for Assessments

5. Other Relevant Information