CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 72-744/S-011

Name: Metoclopramide Oral Solution USP, 5 mg/5 mL

Sponsor: Pharmaceutical Associates, Inc.

Approval Date: September 15, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-011

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-011

APPROVAL LETTER w/ REMS DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 72-744/S-011 **APPROVAL LETTER**

Pharmaceutical Associates, Inc.
Attention: Kaye McDonald
Sr. Director of Regulatory and Product Development
201 Delaware Street
Greenville, SC 29605

Dear Madam:

Please refer to your supplemental ANDA 72-744/S-011 for Metoclopramide Oral Solution USP, 5 mg/5 mL, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA), dated March 30, 2009.

We acknowledge receipt of your submissions dated March 30, April 8, April 15, May 12, June 16, June 30, and August 3, 2009.

This supplemental new drug application provides for a proposed Risk Evaluation and Mitigation Strategy (REMS) for Metoclopramide Oral Solution as requested in our letter dated February 26, 2009.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Metoclopramide Oral Solution USP, 5 mg/5 mL, was approved on May 28, 1991. 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. 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. 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 Metoclopramide Oral Solutions were granted marketing authorization. We consider this information to be "new safety information" as defined in FDAAA.

Your proposed REMS, submitted on March 30, 2009, and amended on August 3, 2009, is appended to this letter, and is approved. The REMS consists of a Medication Guide.

We remind you that you must propose a modification to the approved REMS when you submit a supplemental application.

Prominently identify the submission containing the proposed REMS modifications with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR ANDA 72-744
PROPOSED REMS MODIFICATION

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTER TO HEALTHCARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this ANDA and a copy to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved ANDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Sarah Park, Labeling Reviewer, at (240) 276-8995.

Sincerely,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: REMS documents

ANDA #72-744 - Metoclopramide Oral Solution

Gastrointestinal Agent

Pharmaceutical Associates, Inc.
201 Delaware Street
Greenville, SC 29605
Contact Information: Kaye McDonald
(864) 277-7282 Ext. 3377

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goal of this REMS is to minimize the risk of tardive dyskinesia associated with the long-term use of Metoclopramide Oral Solution.

II. REMS ELEMENTS

A. Medication Guide

Pharmaceutical Associates, Inc. will package extended content labeling containing four (4) copies of the Mediation Guide and an extra copy of the Medication Guide attached to the approved Package Insert (R05/09) with each 16 oz bottle of Metoclopramide Oral Solution USP, 5 mg/5mL. This will permit the pharmacist to distribute a copy of the Medication Guide to each patient receiving the dispensed prescription. The bottle label will inform the pharmacist to dispense the Medication Guide.

Pharmaceutical Associates, Inc. also packages Metoclopramide Oral Solution, 5 mg/5mL unit dose cups. Our unit dose cups are packaged with ten (10) cups in a shrink-wrapped tray. The labeling on the unit dose cups states "INTENDED FOR INSTITUTIONAL IN-PATIENT DISPENSING. IF OTHERWISE DISPENSED, AN APPROPRIATE CHILD-RESISTANT CONTAINER SHOULD BE USED". Since this product is intended for use in a hospital or other health care setting, we are proposing to attach one (1) medication guide to each tray label, which will be on top of the unit dose cups shrink-wrapped tray.

The Medication guide is appended to the REMS.

B. Communication Plan

The REMS for ANDA # 72-744 - Metoclopramide Oral Solution does not include a Communication Plan.

C. Elements To Assure Safe Use

The REMS for ANDA #72-744 - Metoclopramide Oral Solution does not include an Elements to Assure Safe Use.

D. Implementation System

The REMS for ANDA #72-744 - Metoclopramide Oral Solution does not include an Elements to Assure Safe Use and as such, an Implementation System is not required.

E. Timetable for Submission of Assessments

The REMS for ANDA #72-744 - Metoclopramide Oral Solution does not include a Timetable for Submission of Assessments.

Medication Guide

Metoclopramide (met-o-KLO-pra-mide)
Oral Solution USP

Read the Medication Guide that comes with Metoclopramide before you start taking it and each time you get a refill. There may be new information. If you take another product that contains metoclopramide (such as REGLAN tablets, REGLAN ODT, or REGLAN injection), you should read the Medication Guide that comes with that product. Some of the information may be different. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Metoclopramide?

Metoclopramide can cause serious side effects, including:

Abnormal muscle movements called tardive dyskinesia (TD). These movements happen mostly in the face muscles. You can not control these movements. They may not go away even after stopping Metoclopramide. There is no treatment for TD, but symptoms may lessen or go away over time after you stop taking Metoclopramide

Your chances for getting TD go up:

- the longer you take Metoclopramide and the more Metoclopramide you take. You should not take Metoclopramide for more than 12 weeks.
- if you are older, especially if you are a woman
- if you have diabetes

It is not possible for your doctor to know if you will get TD if you take Metoclopramide.

Call your doctor right away if you get movements you can not stop or control, such as:

- lip smacking, chewing, or puckering up your mouth
- frowning or scowling
- sticking out your tongue
- blinking and moving your eyes
- shaking of your arms and legs

Your doctor may decide to stop Metoclopramide.

See the section “What are the possible side effects of Metoclopramide?”

What is Metoclopramide?

Metoclopramide is a prescription medicine used:

- in adults for 4 to 12 weeks to relieve heartburn symptoms with gastroesophageal reflux disease (GERD) when certain other treatments do not work. Metoclopramide relieves daytime heartburn and heartburn after meals. It also helps ulcers in the esophagus to heal.

- to relieve symptoms of slow stomach emptying in people with diabetes. Metoclopramide helps treat symptoms such as nausea, vomiting, heartburn, feeling full long after a meal, and loss of appetite. All these symptoms do not get better at the same time.

It is not known if Metoclopramide is safe and works in children.

Who should not take Metoclopramide?

Do not take Metoclopramide if you:

- have stomach or intestine problems that could get worse with Metoclopramide, such as bleeding, blockage or a tear in the stomach or bowel wall
- have an adrenal gland tumor called a pheochromocytoma
- are allergic to Metoclopramide or anything in it. See the end of this Medication Guide for a list of ingredients in Metoclopramide.
- take medicines that can cause uncontrolled movements, such as medicines for mental illness
- have seizures

What should I tell my doctor before taking Metoclopramide?

Tell your doctor about all your medical conditions, including if you have:

- depression
- Parkinson's disease
- high blood pressure
- kidney problems. Your doctor may start with a lower dose.
- liver problems or heart failure. Metoclopramide may cause your body to hold fluids.
- diabetes. Your dose of insulin may need to be changed.
- breast cancer
- you are pregnant or plan to become pregnant. It is not known if Metoclopramide will harm your unborn baby.
- you are breast-feeding. Metoclopramide can pass into breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you take Metoclopramide.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Metoclopramide and some other medicines may interact with each other and may not work as well, or cause possible side effects. Do not start any new medicines while taking Metoclopramide until you talk with your doctor. **Especially tell your doctor if you take:**

- another medicine that contains Metoclopramide, such as REGLAN tablets, REGLAN ODT.
- a blood pressure medicine
- a medicine for depression, especially an Monoamine Oxidase Inhibitor (MAOI)
- insulin
- a medicine that can make you sleepy, such an anti-anxiety medicine, sleep medicines, and narcotics.

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take Metoclopramide?

- Take Metoclopramide exactly as your doctor tells you. Do not change the dose unless your doctor tells you.
- You should not take Metoclopramide for more than 12 weeks.
- If you take too much Metoclopramide, call your doctor or Poison Control Center right away.

What should I avoid while taking Metoclopramide?

- Do not drink alcohol while taking Metoclopramide. Alcohol may make some side effects of Metoclopramide worse, such as feeling sleepy.
- Do not drive, work with machines, or do dangerous tasks until you know how Metoclopramide affects you. Metoclopramide may cause sleepiness.

What are the possible side effects of Metoclopramide?

Metoclopramide can cause serious side effects, including:

- **Abnormal muscle movements.** See "What is the most important information I need to know about Metoclopramide?"
- **Uncontrolled spasms of your face and neck muscles, or muscles of your body, arms, and legs** (dystonia). These muscle spasms can cause abnormal movements and body positions. These spasms usually start within the first 2 days of treatment. These spasms happen more often in children and adults under age 30.
- **Depression, thoughts about suicide, and suicide.** Some people who take Metoclopramide become depressed. You may have thoughts about hurting or killing yourself. Some people who take Metoclopramide have ended their own lives (committed suicide).
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a very rare but very serious condition that can happen with certain medicines, such as Metoclopramide. NMS can cause death and must be treated in a hospital. Symptoms of NMS include: high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating.
- **Parkinsonism.** Symptoms include slight shaking, body stiffness, trouble moving or keeping your balance. If you already have Parkinson's disease, your symptoms may become worse while you are receiving Metoclopramide.

Call your doctor and get medical help right away if you:

- feel depressed or have thoughts about hurting or killing yourself
- have high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating
- have muscle movements you cannot stop or control
- have muscle movements that are new or unusual

Common side effects of Metoclopramide include:

- feeling restless, sleepy, tired, dizzy, or exhausted

- headache
- confusion
- trouble sleeping

You may have more side effects the longer you take Metoclopramide and the more Metoclopramide you take.

You may still have side effects after stopping Metoclopramide. You may have symptoms from stopping (withdrawal) Metoclopramide such as headaches, and feeling dizzy or nervous.

Tell your doctor about any side effects that bother you or do not go away. These are not all the possible side effects of Metoclopramide.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Metoclopramide?

- Keep Metoclopramide at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Keep Metoclopramide in the bottle it comes in. Keep the bottle closed tightly.

Keep Metoclopramide and all medicines out of the reach of children.

General information about Metoclopramide

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Metoclopramide for a condition for which it was not prescribed. Do not give Metoclopramide to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Metoclopramide. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Metoclopramide that is written for health professionals. For more information, go to www.paipharma.com or call 1-800-845-8210.

What are the ingredients in Metoclopramide?
Active ingredient: Metoclopramide
Inactive ingredients: citric acid, FD&C Yellow No. 6 (Sunset Yellow), flavoring, glycerin, methylparaben, propylparaben, purified water, and sorbitol solution.

R05/09

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-72744	SUPPL-11	PHARMACEUTICAL ASSOC INC DIV BEACH PRODUCTS	METOCLOPRAMIDE HYDROCHLORIDE

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

/s/

GARY J BUEHLER
09/15/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-011

LABELING REVIEW(S)

Labeling Review Branch

Division of Labeling and Program Support
Office of Generic Drugs

Labeling Supplement Review

Application Number: 72-744/S-011

Name of Drug: Metoclopramide Oral Solution USP, 5 mg/5 mL

Applicant: Pharmaceutical Associates, Inc.

Material Reviewed: (specify labeling pieces)

Submission Date(s):

March 30, 2009	REMS submission
April 8, 2009	REMS amendment
April 15, 2009	REMS amendment
May 12, 2009	REMS amendment
June 16, 2009	REMS amendment
June 30, 2009	REMS amendment

Background and Summary

1. Background:
   On February 26, 2009, an IR letter was sent to the firm under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Metoclopramide Oral Solution USP, 5 mg/5 mL to address the risk of tardive dyskinesia associated with the use of this product based on new safety information about this risk. Firm was asked to make safety labeling changes to the insert and propose a Medication Guide. Firm was also asked to propose a Risk Evaluation and Mitigating Strategy (REMS). The insert and Medication Guide were approved on June 30, 2009 under S-010

2. This supplemental application provides for a proposed REMS in response to the February 26, 2009 IR letter.

3. RLD is ANDA 74-703/S-006, Metoclopramide Oral Solution USP, 5 mg/5 mL, by Morton Grove Pharmaceuticals Inc., approved on June 30, 2009.
   Previous RLD (currently discontinued in the Orange Book) was NDA 18-821, Reglan Syrup, which was withdrawn on November 12, 2002.
   RLD for the tablet dosage form is Reglan Tablets, NDA 17-854/S-017 approved July 26, 2004.

4. Patent/Exclusivity Statement: none

Review

The proposed REMS was consulted to the OSE and reviewed by Mary Dempsey, Risk Management Program Coordinator (DRISK). The REMS review signed on June 24, 2009 recommends the following comments to be communicated to the firm.

1. Revise your REMS goal as follows to be consistent with REMS goal for all metoclopramide products:

   > The goal of this REMS is to minimize the risk of tardive dyskinesia associated with long-term use of Metoclopramide Oral Solution.

2. Your proposed REMS does not provide enough detail to determine whether your Medication Guide distribution procedure is acceptable. Revise and resubmit a Medication Guide distribution procedure that ensures sufficient numbers of Medications Guides will be provided with the product such that each patient will receive a printed, hard-copy of the approved Medication Guide. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

   - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.

   - A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

3. We remind you of the requirement to comply with 21 CFR 208.24. A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use): "Dispense the enclosed Medication Guide to each patient." or "Dispense the accompanying Medication Guide to each patient."

4. Please see appended REMS proposal for additional track changes corresponding to comments in this review.

Recommendation

The submitted REMS is not acceptable. The comments recommended by OSE/DRISK are to be communicated to the firm. The firm is asked to respond as a **REMS-AMENDMENT.**

{see appended electronic signature}

Sarah Park
Labeling Reviewer

Supervisory Comment/Concurrence:

{see appended electronic signature}

Koung Lee
Team Leader

Following this page, 2 pages withheld in full - (b)(4) draft labeling.

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

/s/

Soojung Sarah Park
7/15/2009 06:06:20 PM
LABELING REVIEWER

Koung Lee
7/17/2009 10:28:27 AM
LABELING REVIEWER

Labeling Review Branch

Division of Labeling and Program Support
Office of Generic Drugs

Labeling Supplement Review

Application Number: 72-744/S-011

Name of Drug: Metoclopramide Oral Solution USP, 5 mg/5 mL

Applicant: Pharmaceutical Associates, Inc.

Material Reviewed: (specify labeling pieces)

Submission Date(s):

August 3, 2009	**REMS amendment** **Resubmission of Medication Guide approved on June 30, 2009 (draft)**

Previous Submissions:

March 30, 2009	REMS submission
April 8, 2009	REMS amendment
April 15, 2009	REMS amendment
May 12, 2009	REMS amendment
June 16, 2009	REMS amendment
June 30, 2009	REMS amendment

Background and Summary

1. Background:
   On February 26, 2009, an IR letter was sent to the firm under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Metoclopramide Oral Solution USP, 5 mg/5 mL to address the risk of tardive dyskinesia associated with the use of this product based on new safety information about this risk. Firm was asked to make safety labeling changes to the insert and propose a Medication Guide. Firm was also asked to propose a Risk Evaluation and Mitigating Strategy (REMS). The insert and Medication Guide were approved on June 30, 2009 under S-010

2. This supplemental application provides for a proposed REMS in response to the February 26, 2009 IR letter.

3. RLD is ANDA 74-703/S-006, Metoclopramide Oral Solution USP, 5 mg/5 mL, by Morton Grove Pharmaceuticals Inc., approved on June 30, 2009.
   Previous RLD (currently discontinued in the Orange Book) was NDA 18-821, Reglan Syrup, which was withdrawn on November 12, 2002.
   RLD for the tablet dosage form is Reglan Tablets, NDA 17-854/S-017 approved July 26, 2004.

4. Patent/Exclusivity Statement: none

Review

The proposed REMS was consulted to the OSE and reviewed by Mary Dempsey, Risk Management Program Coordinator (DRISK). The REMS review signed on June 24, 2009 recommended the following comments to be communicated to the firm.

1. Revise your REMS goal as follows to be consistent with REMS goal for all metoclopramide products:

   > The goal of this REMS is to minimize the risk of tardive dyskinesia associated with long-term use of Metoclopramide Oral Solution.

2. Your proposed REMS does not provide enough detail to determine whether your Medication Guide distribution procedure is acceptable. Revise and resubmit a Medication Guide distribution procedure that ensures sufficient numbers of Medications Guides will be provided with the product such that each patient will receive a printed, hard-copy of the approved Medication Guide. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

   - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
   - A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

3. We remind you of the requirement to comply with 21 CFR 208.24. A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use): "Dispense the enclosed Medication Guide to each patient." or "Dispense the accompanying Medication Guide to each patient."

4. Please see appended REMS proposal for additional track changes corresponding to comments in this review.

The firm submitted revised REMS on August 3, 2009. The firm proposed to "package extended content labeling containing four (4) copies of the Mediation Guide and an extra copy of the Medication Guide attached to the approved Package Insert (R05/09) with each 16 oz bottle." For the unit dose cups (10 mL) packaged in 10 cups per tray, the firm proposed "one (1) medication guide to each tray label." After email correspondences between Mary Dempsey of DRISK and Sarah Park and Koung Lee of OGD, DRISK proposed a change to "a sufficient quantity of medication guides with each unit dose tray..." The "Medication Guide" section of "REMS ELEMENTS" as proposed by DRISK is as follows:

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be provided with each Metoclopramide Oral Solution prescription.

Pharmaceutical Associates, Inc. will package extended content labeling containing four (4) copies of the Mediation Guide and an extra copy of the Medication Guide attached to the approved Package Insert (R05/09) with each 16 oz bottle of Metoclopramide Oral Solution USP, 5 mg/5mL. This will permit the pharmacist to distribute a copy of the Medication Guide to each patient receiving the dispensed prescription. The bottle label will inform the pharmacist to dispense the Medication Guide.

Pharmaceutical Associates, Inc. also packages Metoclopramide Oral Solution, 5 mg/5mL unit dose cups. Our unit dose cups are packaged with ten (10) cups in a shrink-wrapped tray. Pharmaceutical Associates, Inc. will provide a sufficient quantity of medication guides with each unit dose tray for distribution to the patient or the patient's representative at the initiation of therapy and then at least once a month for as long as treatment continues.

The Medication guide is appended to the REMS.

The firm will be ask to revise their REMS as recommended by DRISK and submit a revised REMS as a CBE supplement.

The August 3, 2009 REMS submission was also reviewed along with NDA 17-854 (Reglan Tablets), NDA 21-793 (Reglan Orally Disintegrating Tablets), and NDA 17862 (Reglan Injection) by Dr. Tamara Johnson of the Division of Gastroenterology Products, and signed by Dr. Nancy Snow on August 26, 2006. The Division of Gastroenterology Products found Pharmaceutical Associates' REMS acceptable.

Recommendation

The REMS submitted on August 3, 2009, is acceptable with comments. The firm is asked to revise their REMS as recommended by DRISK and submit a revised REMS as a CBE supplement.

{see appended electronic signature}

Sarah Park
Labeling Reviewer

Supervisory Comment/Concurrence:

{see appended electronic signature}

Koung Lee
Team Leader

AMENDMENT TO SUPPLEMENT - 10 FOR ANDA #72-744
PROPOSED REMS AMENDMENT

ANDA #72-744 - Metoclopramide Oral Solution

Gastrointestinal Agent

Pharmaceutical Associates, Inc.
201 Delaware Street
Greenville, SC 29605
Contact Information: Kaye McDonald
(864) 277-7282 Ext. 3377

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goal of this REMS is to minimize the risk of tardive dyskinesia associated with the long-term use of Metoclopramide Oral Solution.

II. REMS ELEMENTS

A. Medication Guide

Pharmaceutical Associates, Inc. will package extended content labeling containing four (4) copies of the Mediation Guide and an extra copy of the Medication Guide attached to the approved Package Insert (R05/09) with each 16 oz bottle of Metoclopramide Oral Solution USP, 5 mg/5mL. This will permit the pharmacist to distribute a copy of the Medication Guide to each patient receiving the dispensed prescription. The bottle label will inform the pharmacist to dispense the Medication Guide.

Pharmaceutical Associates, Inc. also packages Metoclopramide Oral Solution, 5 mg/5mL unit dose cups. Our unit dose cups are packaged with ten (10) cups in a shrink-wrapped tray. The labeling on the unit dose cups states "INTENDED FOR INSTITUTIONAL IN-PATIENT DISPENSING. IF OTHERWISE DISPENSED, AN APPROPRIATE CHILD-RESISTANT CONTAINER SHOULD BE USED". Since this product is intended for use in a hospital or other health care setting, we are proposing to attach one (1) medication guide to each tray label, which will be on top of the unit dose cups shrink-wrapped tray.

The Medication guide is appended to the REMS.

B. Communication Plan

The REMS for ANDA # 72-744 - Metoclopramide Oral Solution does not include a Communication Plan.

AMENDMENT TO SUPPLEMENT - 10 FOR ANDA #72-744
PROPOSED REMS AMENDMENT

C. Elements To Assure Safe Use

The REMS for ANDA #72-744 - Metoclopramide Oral Solution does not include an Elements to Assure Safe Use.

D. Implementation System

The REMS for ANDA #72-744 - Metoclopramide Oral Solution does not include an Elements to Assure Safe Use and as such, an Implementation System is not required.

E. Timetable for Submission of Assessments

The REMS for ANDA #72-744 - Metoclopramide Oral Solution does not include a Timetable for Submission of Assessments.

ANDA #72-744 - Metoclopramide Oral Solution

Gastrointestinal Agent

Pharmaceutical Associates, Inc.
201 Delaware Street
Greenville, SC 29605
Contact Information: Kaye McDonald
(864) 277-7282 Ext. 3377

APPENDIX B – REMS SUPPORTING DOCUMENT

1. Background

Based on new safety information received from the FDA on February 26, 2009, recently published analyses suggest that Metoclopramide has surpassed Haloperidol as the most common drug-induced cause of movement disorders. The FDA has become aware of continued spontaneous reports of tardive dyskinesia associated with Metoclopramide use. Exposure greater than 12 weeks was evident in a majority of these reports.

2. Goals

The goal of this REMS is to minimize the risk of tardive dyskinesia associated with long-term use of Metoclopramide Oral Solution.

3. Supporting Information on Proposed REMS Elements

a. Additional Potential Elements

i. Medication Guide – included

ii. Patient Package Insert – not necessary

iii. Communication Plan – not necessary

b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk. – included
A medication guide to patients to make patient aware of the risk and to discuss the risk with their health care provider

c. Implementation system – not necessary

d. Timetable for assessment of the REMS – not necessary

4. Information Needed for Assessments – not necessary

5. Other Relevant Information – none available

Medication Guide

Metoclopramide (met-o-KLO-pra-mide)
Oral Solution USP

Read the Medication Guide that comes with Metoclopramide before you start taking it and each time you get a refill. There may be new information. If you take another product that contains metoclopramide (such as REGLAN tablets, REGLAN ODT, or REGLAN injection), you should read the Medication Guide that comes with that product. Some of the information may be different. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Metoclopramide?

Metoclopramide can cause serious side effects, including:

Abnormal muscle movements called tardive dyskinesia (TD). These movements happen mostly in the face muscles. You can not control these movements. They may not go away even after stopping Metoclopramide. There is no treatment for TD, but symptoms may lessen or go away over time after you stop taking Metoclopramide

Your chances for getting TD go up:

- the longer you take Metoclopramide and the more Metoclopramide you take. You should not take Metoclopramide for more than 12 weeks.
- if you are older, especially if you are a woman
- if you have diabetes

It is not possible for your doctor to know if you will get TD if you take Metoclopramide.

Call your doctor right away if you get movements you can not stop or control, such as:

- lip smacking, chewing, or puckering up your mouth
- frowning or scowling
- sticking out your tongue
- blinking and moving your eyes
- shaking of your arms and legs

Your doctor may decide to stop Metoclopramide.

See the section “What are the possible side effects of Metoclopramide?”

What is Metoclopramide?

Metoclopramide is a prescription medicine used:

- in adults for 4 to 12 weeks to relieve heartburn symptoms with gastroesophageal reflux disease (GERD) when certain other treatments do not work. Metoclopramide relieves daytime heartburn and heartburn after meals. It also helps ulcers in the esophagus to heal.
- to relieve symptoms of slow stomach emptying in people with diabetes. Metoclopramide helps treat symptoms such as nausea, vomiting, heartburn, feeling full long after a meal, and loss of appetite. All these symptoms do not get better at the same time.

It is not known if Metoclopramide is safe and works in children.

Who should not take Metoclopramide?

Do not take Metoclopramide if you:

- have stomach or intestine problems that could get worse with Metoclopramide, such as bleeding, blockage or a tear in the stomach or bowel wall
- have an adrenal gland tumor called a pheochromocytoma
- are allergic to Metoclopramide or anything in it. See the end of this Medication Guide for a list of ingredients in Metoclopramide.
- take medicines that can cause uncontrolled movements, such as medicines for mental illness
- have seizures

What should I tell my doctor before taking Metoclopramide?

Tell your doctor about all your medical conditions, including if you have:

- depression
- Parkinson's disease
- high blood pressure
- kidney problems. Your doctor may start with a lower dose.
- liver problems or heart failure. Metoclopramide may cause your body to hold fluids.
- diabetes. Your dose of insulin may need to be changed.
- breast cancer
- you are pregnant or plan to become pregnant. It is not known if Metoclopramide will harm your unborn baby.
- you are breast-feeding. Metoclopramide can pass into breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you take Metoclopramide.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Metoclopramide and some other medicines may interact with each other and may not work as well, or cause possible side effects. Do not start any new medicines while taking Metoclopramide until you talk with your doctor.
Especially tell your doctor if you take:

- another medicine that contains Metoclopramide, such as REGLAN tablets, REGLAN ODT.
- a blood pressure medicine
- a medicine for depression, especially an Monoamine Oxidase Inhibitor (MAOI)
- insulin
- a medicine that can make you sleepy, such an anti-anxiety medicine, sleep medicines, and narcotics.

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take Metoclopramide?

- Take Metoclopramide exactly as your doctor tells you. Do not change the dose unless your doctor tells you.

- You should not take Metoclopramide for more than 12 weeks.
- If you take too much Metoclopramide, call your doctor or Poison Control Center right away.

What should I avoid while taking Metoclopramide?

- Do not drink alcohol while taking Metoclopramide. Alcohol may make some side effects of Metoclopramide worse, such as feeling sleepy.
- Do not drive, work with machines, or do dangerous tasks until you know how Metoclopramide affects you. Metoclopramide may cause sleepiness.

What are the possible side effects of Metoclopramide?

Metoclopramide can cause serious side effects, including:

- **Abnormal muscle movements.** See "What is the most important information I need to know about Metoclopramide?"
- **Uncontrolled spasms of your face and neck muscles, or muscles of your body, arms, and legs** (dystonia). These muscle spasms can cause abnormal movements and body positions. These spasms usually start within the first 2 days of treatment. These spasms happen more often in children and adults under age 30.
- **Depression, thoughts about suicide, and suicide.** Some people who take Metoclopramide become depressed. You may have thoughts about hurting or killing yourself. Some people who take Metoclopramide have ended their own lives (committed suicide).
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a very rare but very serious condition that can happen with certain medicines, such as Metoclopramide. NMS can cause death and must be treated in a hospital. Symptoms of NMS include: high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating.
- **Parkinsonism.** Symptoms include slight shaking, body stiffness, trouble moving or keeping your balance. If you already have Parkinson's disease, your symptoms may become worse while you are receiving Metoclopramide.

Call your doctor and get medical help right away if you:

- feel depressed or have thoughts about hurting or killing yourself
- have high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating
- have muscle movements you cannot stop or control
- have muscle movements that are new or unusual

Common side effects of Metoclopramide include:

- feeling restless, sleepy, tired, dizzy, or exhausted
- headache
- confusion
- trouble sleeping

You may have more side effects the longer you take Metoclopramide and the more Metoclopramide you take.

You may still have side effects after stopping Metoclopramide. You may have symptoms from stopping (withdrawal) Metoclopramide such as headaches, and feeling dizzy or nervous.

Tell your doctor about any side effects that bother you or do not go away. These are not all the possible side effects of Metoclopramide.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Metoclopramide?

- Keep Metoclopramide at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Keep Metoclopramide in the bottle it comes in. Keep the bottle closed tightly.

Keep Metoclopramide and all medicines out of the reach of children.

General information about Metoclopramide

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Metoclopramide for a condition for which it was not prescribed. Do not give Metoclopramide to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Metoclopramide. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Metoclopramide that is written for health professionals. For more information, go to www.paipharma.com or call 1-800-845-8210.

What are the ingredients in Metoclopramide?
Active ingredient: Metoclopramide
Inactive ingredients: citric acid, FD&C Yellow No. 6 (Sunset Yellow), flavoring, glycerin, methylparaben, propylparaben, purified water, and sorbitol solution.

R05/09

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
ANDA 72744	SUPPL 11	PHARMACEUTICAL ASSOC INC DIV BEACH PRODUCTS	METOCLOPRAMIDE HYDROCHLORIDE

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/s/

SOOJUNG S PARK
08/29/2009

KOUNG U LEE
08/31/2009
For Wm Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-011

MEDICAL REVIEW(S)

DIVISION OF GASTROENTEROLOGY PRODUCTS
MEDICAL OFFICER'S REVIEW

FDAAA SAFETY REVIEW OF REMS ELEMENTS FOR METOCLOPRAMIDE REFERENCE LISTED DRUGS

Drug Product/Formulation/ Sponsor Name/ NDA or ANDA # (Supplement #)	**Indications:**	**Date of Submission**	**FDAAA Action Date**
Reglan Tablets/Alaven Pharmaceuticals/ NDA 017854 (052)	• Diabetic Gastroparesis (Diabetic Gastric Stasis) • Symptomatic Gastroesophageal Reflux Disease (GERD)	March 25, 2009	August 25, 2009
Reglan Oral Disintegrating Tablets/Alaven Pharmaceuticals/ NDA 021793 (005)		March 25, 2009	
Metoclopramide oral solution/ Morton Grove Pharmaceuticals/ ANDA 074703 (S-007)		March 27, 2009	
Metoclopramide oral solution/ Silarx Pharmaceuticals Inc/ ANDA 073680 (S-018)		March 17, 2009	
Metoclopramide oral solution/Pharmaceutical Associates Inc)/ ANDA 072744 (S-011)		March 31, 2009	
Metoclopramide oral solution/ ANI Pharmaceuticals Inc/ ANDA 071402 (S-008)		March 27, 2009	
Reglan Injection/ Baxter Healthcare Corp/ NDA 017862 (063)	• Diabetic gastroparesis (diabetic gastric stasis) • Prevention of nausea and vomiting associated with emetogenic cancer chemotherapy • Prevention of postoperative nausea and vomiting • Small bowel intubation • Radiological examination	July 16, 2009	August 25, 2009

Review completed: **August 4, 2009**
Reviewer: **Tamara Johnson, MD, MS**

Purpose

As authorized under the Food and Drug Administration Amendments Act of 2007 (FDAAA), a class labeling and Risk Evaluation and Mitigation Strategy (REMS) safety initiative for metoclopramide products was initiated, based on concerns related to the risk of developing tardive dyskinesia (TD) with long-term use. The REMS documents for the above listed reference listed drugs (RLD) have been reviewed in accordance with the current product labeling (Package Inserts (PI)) and the recent FDA-proposed boxed warning and warning section language regarding the risk of TD. Because the original RLD for oral solutions has been withdrawn from marketing, the four currently marketed generic oral solutions were reviewed as RLDs.

This review reflects the perspective of the Division of Gastroenterology Products (DGP) on the REMS, and was completed subsequent to reviews performed by the Office of Safety Evaluation's Division of Risk Management (DRISK). Clinical review of the associated medication guides and PI's is included in the June 30, 2009 document co-authored by this reviewer and Dr. Chris Leptak, DGP.

Materials Reviewed

- REMS documents, including medication guides, submitted to NDA's 17-854, 17-862, 21-793 and ANDA's 71-402, 72-744, 73-680, 74-703 in response to the FDA REMS memorandum, dated February 26, 2009.
- Package Insert Labeling submitted to NDA's 17-854, 17-862, 21-793 and ANDA's 71-402, 72-744, 73-680, 74-703 in response to the FDA REMS memorandum, dated February 26, 2009.
- Consultation Reviews completed by Sharon Mills, Mary Dempsey, and Claudia Karwoski of DRISK.

Background

The increasing concern regarding the risk of tardive dyskinesia with prolonged use of metoclopramide has prompted this safety initiative under FDAAA. The medical literature demonstrates that metoclopramide is now the leading cause of drug-induced movement disorders.[1,2] Since the time of cisapride's withdrawal from the US market in 2000, metoclopramide utilization has increased, especially for treatment of symptomatic GERD.[3,4] Adverse event reports submitted to the FDA continue to link tardive dyskinesia to metoclopramide use. The above described new safety information about the risk of tardive dyskinesia authorizes FDA to require a REMS for approved drugs.

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[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.

[4] Shaffer D, Butterfield M, Pamer C, Corken Mackey A. Tardive dyskinesia risks and metoclopramide use before and after US market withdrawal of cisapride. J Am Pharm Assoc 2004;44:661-665.

REMS Review

I. Goal

The REMS goal statements were reviewed from each sponsor and harmonized to provide the best rendition. The agreed upon REMS goal statement follows:

> *The goal of this REMS is to minimize the risk of tardive dyskinesia associated with the long-term use of* XXXXXX (insert metoclopramide product tradename).

II. REMS Elements

DGP concurs with the recommendations from DRISK's review of the elements of the REMS for the above listed metoclopramide RLD products. The Division has the following additional requirements regarding the REMS elements proposed for the branded products.

a. Reglan tablets (NDA 017854) and Reglan ODT (NDA 021793)
   i. The sponsor (Alaven) has added the statement, "Medication Guide must be provided with each prescription", on bottle labels of all strengths of Reglan tablets. This differs from the recommended language consistent with 21 CFR 208.24 that was communicated to the sponsor in FDA letter dated July 7, 2009. The sponsor must revise the statement to reflect how the med guide is provided, i.e., "enclosed in" or "accompanying" the container. As the sponsor has already started printing the container without final FDA approval, it was agreed that they would make this change upon the next container printing.

b. Reglan IV (NDA 017862)
   i. The sponsor (Baxter) seeks to disseminate the medication guide through (b) (4) means only. This method of communication is not accessible to all healthcare professionals, patient caregivers, and patients. The sponsor is required to include physical medication guides, and consider accompanying tearpads of the medication guide to complement the (b) (4) communication method.
   ii. The sponsor seeks to perform only (b) (4) (b) (4) earmarks. Although the sponsor reasonably explains why (b) (4) are targeted for (b) (4) rather than (b) (4) there is no justification for (b) (4) The sponsor must adhere to the (b) (4)
   iii. The carton and container labeling conforms to the recommended language consistent with 21 CFR 208.24, "Dispense the accompanying Medication Guide to each patient."

Conclusion

This reviewer finds the REMS elements appropriate to meet the goal of this metoclopramide class REMS, once the above noted requirements have been addressed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21793	SUPPL-5	ALAVEN PHARMACEUTICAL LLC	REGLAN RPT(METOCLOPRAMIDE)5/10 MG TABS
NDA-17854	SUPPL-52	ALAVEN PHARMACEUTICAL LLC	REGLAN
NDA-17862	SUPPL-62	BAXTER HEALTHCARE CORP ANESTHESIA CRITICAL CARE	REGLAN

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/s/

TAMARA N JOHNSON
08/25/2009

NANCY C SNOW
08/26/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-011

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 22, 2009
To:	Donna Griebel, MD, Director Division of Gastrointestinal Products (DGP)
Through:	Gary Buehler, Director Office of Generic Drugs (OGD) Claudia Karwoski, Pharm.D., Director (Acting) Division of Risk Management (DRISK)
From:	Mary Dempsey, Risk Management Program Coordinator (DRISK)
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Metoclopramide Oral Solution
Application Type/Number:	ANDA 72-744
Applicant/sponsor:	Pharmaceutical Associates, Inc..
OSE RCM #:	2009-604

1 INTRODUCTION

This memorandum is in response to a request by the DGP to review the proposed REMS for the innovator and generic metoclopramide products. The comments below reflect our review of the proposed REMS for Metoclopramide Oral Solution. Please send these comments to the sponsor and request the sponsor provide a response to these comments and questions within 2 weeks upon receipt. Please let us know if you would like a meeting to discuss before sending. DRISK's review of the draft Medication Guide was sent to DGP in a separate memorandum dated April 24, 2009.

2 MATERIAL REVIEWED

- ANDA 72-744 Metoclopramide Oral Solution SLC and REMS Notification Letter, dated February 26, 2009
- Pharmaceutical Associates proposed REMS submitted March 15, 2009

3 CONCLUSION/RECOMMENDATIONS

DRISK concurs with the elements of the REMS and with the agreed upon goal for all metoclopramide REMS as the following:

> The goal of this REMS is to minimize the risk of tardive dyskinesia associated with the long-term use of XXXXX (insert metoclopramide product trade name).

We have the following comments for the Sponsor on the proposed REMS.

Comments to Pharmaceutical Associates:

1. Revise your REMS goal as follows to be consistent with REMS goal for all metoclopramide products:

   > The goal of this REMS is to minimize the risk of tardive dyskinesia associated with long-term use of Metoclopramide Oral Solution.

2. Your proposed REMS does not provide enough detail to determine whether your Medication Guide distribution procedure is acceptable. Revise and resubmit a Medication Guide distribution procedure that ensures sufficient numbers of Medications Guides will be provided with the product such that each patient will receive a printed, hard-copy of the approved Medication Guide. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

   - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.

- A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

3. We remind you of the requirement to comply with 21 CFR 208.24. A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use): "Dispense the enclosed Medication Guide to each patient." or "Dispense the accompanying Medication Guide to each patient."

4. Please see appended REMS proposal for additional track changes corresponding to comments in this review.

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/s/

Mary Dempsey
6/24/2009 11:12:31 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
6/24/2009 11:26:31 AM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III
Division of Gastroenterology Products

NDA #:	17-854
Product:	Reglan (metoclopramide tablets, USP) Tablets
SPONSOR:	Alaven Pharmaceutical LLC.
NDA #:	21-793
Product:	Reglan ODT (metoclopramide) Orally Disintegrating Tablets
SPONSOR:	Alaven Pharmaceutical LLC.
ANDA#:	74-703
Product:	Metoclopramide Oral Solution
SPONSOR:	Morton Grove Pharmaceuticals, Inc.
ANDA#:	71-402
Product:	Metoclopramide Oral Solution
SPONSOR:	ANI Pharmaceuticals, Inc.
ANDA#:	72-744
Product:	Metoclopramide Oral Solution
SPONSOR:	Pharmaceutical Associates, Inc.
ANDA#:	73-680
Product:	Metoclopramide Oral Solution
SPONSOR:	Silarx Pharmaceuticals, Inc.
NDA #:	22-246
Products:	Metozolv ODT (metoclopramide) Orally Disintegrating Tablets
SPONSOR:	Wilmington Pharmaceuticals
FROM:	Joyce Korvick, MD MPH Deputy Director of Safety
DATE:	February 26, 2009

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 authorize FDA to require the submission of a REMS for an approved drug if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

Reglan Tablets and Reglan ODT Orally Disintegrating Tablets were approved on December 30, 1980 and June 10, 2005, respectively. The Metoclopramide Oral Solution products were approved on May 28, 1991 (ANDA 72-744), October 27, 1992 (ANDA 73-680), June 25, 1993 (ANDA 71-402), and October 31, 1997 (ANDA 74-703). The NDA for Metozolv ODT, received January 29, 2008, is currently under review. Current product labeling for approved metoclopramide products 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 Tablets, Reglan ODT Orally Disintegrating Tablets, and the four Metoclopramide oral solution products referenced above were granted marketing authorization. We consider this information to be "new safety information" as defined in FDAAA.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of metoclopramide outweigh its risks. In reaching this determination we considered the following:

A. Drug utilization data indicate that metoclopramide is used in about 2 million patients in the US and the number of patients using the product has been rising. In addition, most of the uses from the years 2002 to 2007 were for gastroesophageal reflux disease (GERD).[4] Although a relatively small proportion of metoclopramide use was for gastroparesis, metoclopramide dominated the market share for use in this condition.

B. Metoclopramide is approved for the treatment of patients with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy, and

[4] For the purpose of this memo, patients with the labeled indication "gastroesophageal reflux who fail to respond to conventional therapy" are considered to have "gastroesophageal reflux disease" or GERD.

for diabetic gastroparesis (diabetic gastric stasis). The treatment of these patients includes the healing of esophageal ulcers and erosions in addition to symptomatic treatment. Ulcers and erosions can progress to perforations of the esophagus, serious bleeding and potentially cancer of the esophagus. Diabetic gastric stasis is a serious condition that can lead to weight loss due to the inability to ingest an adequate amount of food, malabsorption, and malnutrition. This is a serious issue especially in fragile diabetics making it difficult to control the patient's blood sugar.

C. Patients with symptomatic gastroesophageal reflux will experience fewer symptoms and, in addition, those with esophageal erosions that are healed may not experience serious bleeding and perforation. Short-term treatment has not been shown to prevent esophageal cancer.

Patients with diabetic gastroparesis who respond to this therapy will have the ability to eat and retain a normal diet volume. In addition, symptoms such as nausea, vomiting, abdominal pain and bloating will improve. These improvements may lead to better nutrition and better blood sugar control.

D. Symptomatic Gastroesophageal Reflux: Metoclopramide is approved for short-term (4-12 weeks) treatment in adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy. In addition, for patients with gastroesophageal erosions, 12 weeks of therapy has been successful. Therapy longer than 12 weeks has not been evaluated and is not recommended.

Diabetic Gastroparesis: Metoclopramide is approved for the relief of symptoms associated with diabetic gastroparesis. Product labeling recommends treatment for "two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation". It further states that since diabetic gastric stasis is frequently recurrent, metoclopramide "should be reinstituted at the earliest manifestation." This implies that metoclopramide may be used episodically in these patients.

E. 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 than 12 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.

F. The drug metoclopramide, found in Reglan Tablets, Reglan ODT Orally Disintegrating Tablets, and the four Metoclopramide Oral Solution products referenced above, and the pending application for Metozolv ODT, is not an NME.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that metoclopramide poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of metoclopramide. FDA has determined that metoclopramide is a product that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use metoclopramide. FDA has also determined that metoclopramide is a product for which patient labeling could help prevent serious adverse events.

The elements of the REMS for Reglan Tablets, Reglan ODT Orally Disintegrating Tablets, and Metozolv ODT will be a Medication Guide and a timetable for submission of assessments of the REMS. The elements of the REMS for the four Metoclopramide Oral Solution products referenced above will be a Medication Guide only. To protect the public health, FDA is requiring all sponsors of approved metoclopramide products to submit a proposed REMS within 30 days of receipt of FDA's notification that a REMS for metoclopramide is required. Wilmington Pharmaceuticals, the sponsor of the pending NDA for Metozolv ODT, will need to submit a proposed REMS to its application before evaluation of the NDA can continue.

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[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.

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/s/

Joyce Korvick
2/26/2009 09:40:52 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

ANDA 72-744

Pharmaceutical Associates, Inc.
Attention: Kay McDonald
201 Delaware Street
Greenville, SC 29605

Dear Madam:

Please refer to your Abbreviated New Drug Application ANDA 72-744 for Metoclopramide Oral Solution USP, 5 mg/5 mL, which was approved on May 28, 1991.

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 to 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.

Section 505(o)(4) also authorizes FDA to require the holder of an approved application under section 505(j) (an abbreviated new drug application or ANDA) to make safety related label changes based upon new safety information if the same drug approved under section 505(b) is not currently marketed. You are the holder of ANDA 72-744 which references a drug approved under section 505(b) that is withdrawn and not currently marketed.

Your ANDA for Metoclopramide Oral Solution USP, 5 mg/5 mL was approved on May 28, 1991. 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

[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.

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 your ANDA was approved. 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 Metoclopramide Oral Solution USP, 5 mg/5 mL. We have also determined that 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 Metoclopramide Oral Solution USP, 5 mg/5 mL 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~~

[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.

~~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 Metoclopramide Oral Solution USP, 5 mg/5 mL. 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 Metoclopramide Oral Solution USP, 5 mg/5 mL 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.

Include labeling in both Microsoft Word format and final printed labeling in PDF format. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

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 Metoclopramide Oral Solution USP, 5 mg/5 mL 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 Metoclopramide Oral Solution USP, 5 mg/5 mL poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe use of Metoclopramide Oral Solution USP, 5 mg/5 mL. FDA has determined that Metoclopramide Oral Solution USP, 5 mg/5 mL has 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 Metoclopramide Oral Solution USP, 5 mg/5 mL. FDA has determined that Metoclopramide Oral Solution USP, 5 mg/5 mL is a product 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 Metoclopramide Oral Solution USP, 5 mg/5 mL.

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 Metoclopramide Oral Solution USP, 5 mg/5 mL. 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).

If you do not submit electronically, please send 5 copies of your proposed REMS and REMS Supporting Document as an amendment to your ANDA. 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 ANDA 72-744
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 Sarah Park, Labeling Reviewer, at 240-276-8995.

Sincerely,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
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

If a Timetable for Submission of Assessments is included in the proposed REMS, include the following:

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

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

/s/

Robert L. West
2/26/2009 01:03:35 PM
Deputy Director, for Gary Buehler

pai Pharmaceutical Associates, Inc.

March 19, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, MD 20855

NEW CORRES
N/Mc

RE: ANDA #72-744 – Metoclopramide Oral Solution USP, 5 mg/5 mL

Dear Madam/Sir:

Pharmaceutical Associates, Inc is responding to the agency letter dated February 26, 2009 regarding ANDA #72-744 - Metoclopramide Oral Solution USP, 5 mg/5 mL.

As outlined in the agency letter, the package insert needs to be updated with new labeling revisions and a medication guide must be developed for ANDA #72-744 - Metoclopramide Oral Solution USP, 5 mg/5 mL. The submission will be submitted electronically as an e-Labeling submission - "Supplement Changes Being Effected - (CBE 30)" and the proposed Risk Evaluation and Mitigation Strategy (REMS) will be submitted electronically as a "New Supplement for ANDA #72-744". At this time, we will not be able to submit the changes as requested within 30 days and would like to request a filing extension with the agency.

Enclosed in the submission is FDA Form 356h.

If you have any questions or need additional information, please contact Kaye McDonald at (864) 277-7282, extension 3377 or by fax (864) 299-6431.

Best Regards,

Kaye McDonald

Kaye McDonald
Pharmaceutical Associates, Inc
Sr. Director of Regulatory and Product Development

RECEIVED
MAR 20 2009
OGD

Contract Sales
5220 South Manhattan Avenue
Tampa, FL 33611
Phone: (800) 322-8210 ext. 214
Fax: (813) 839-4665

Customer Service/Shipping
1700 Perimeter Road
Greenville, SC 29605
Phone: (864) 277-7282
Fax: (864) 277-8045

Regulatory/Purchasing
201 Delaware Street
Greenville, SC 29605
Phone: (864) 277-7282
Fax: (864) 299-6431

pai Pharmaceutical Associates, Inc.

March 30, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, MD 20855

NDA NO. 72-744 REF NO. SCS010
NDA SUPPL. FOR Cont. Rv

RE: NEW SUPPLEMENT FOR ANDA #72-744
(METOCLOPRAMIDE ORAL SOLUTION USP, 5 MG/5 ML)
PROPOSED REMS

Dear Sir/Madam:

Pharmaceutical Associates, Inc is responding to the agency letter dated February 26, 2009, a telephone conversation dated March 19, 2009, and a follow-up conversation dated March 26, 2009; regarding ANDA #72-744 - Metoclopramide Oral Solution USP, 5 mg/5 mL.

Enclosed in the submission are FDA Form 356h, a Proposed Risk Evaluation and Mitigation Strategy (REMS), Appendix B - REMS Supporting Document, and a Medication Guide provided in hardcopy (5 additional copies as indicated in the agency letter) for Metoclopramide Oral Solution USP.

As outlined in the agency letter, the Medication Guide was developed under 21 CRF Part 208 and in accordance with safety labeling changes under 505-1. The medication guide will be attached to the Tray Label for Unit Dose Dispensing (Institutional Use Only) and incorporated on the Package Insert (16 oz retail package) with notice on the revised bottle label to the pharmacist to provide the medication guide to the patient upon dispensing. Upon FDA approval of the Medication Guide, we will incorporate the black box and the new Tardive Dyskinesia warning to the Package Insert. The package insert labeling changes will be submitted electronically as a Prior Approval Supplement and will include labeling in Microsoft Word format, final printed labeling in PDF format, and a side-by-side comparison.

If you have any questions or need additional information, please contact Kaye McDonald at (864) 277-7282, extension 3377 or by fax (864) 299-6431.

Best Regards,

Kaye McDonald

Kaye McDonald
Pharmaceutical Associates, Inc
Sr. Director of Regulatory and Product Development

RECEIVED
MAR 31 2009
OGD

Contract Sales
5220 South Manhattan Avenue
Tampa, FL 33611
Phone: (800) 322-8210 ext. 214
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Greenville, SC 29605
Phone: (864) 277-7282
Fax: (864) 299-6431

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Nina Ton, Pharm.D. Safety Regulatory Manager OSE	Kristen Everett, Safety Regulatory Manager, DGP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 3, 2009		multiple- see below		March 17, 2009 (earliest submission)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
metoclopramide class	FDAAA	motility modifiers	May 1, 2009

NAME OF FIRM: Alaven Pharm., ANI, Silarx, Morton Grove, Pharmaceutical Associates

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DGP and OGD request your expertise in the review of the medication guides and REMS documents submitted for the products listed below. EDR links, where available, are provided for the submissions. In addition, package inserts, MGs, and REMS documents will be available in the GI eRoom (Safety folder, REMS/FDAAA Safety Labeling under review, metoclopramide subfolder). The class language that needs to be harmonized across the medication guides is the Boxed warning, and the Tardive Dyskinesia subsection under Warnings (this language is also provided in the supplement request letter sent to the sponsors). The REMS documents should also be fairly similar in that the REMS goal should be the same; however, sponsors may have different methods of distributing the medication guide.

ANDA 71-402ANI (oral syrup) submitted: 3/26/09 - insert, med guide, REMS (missing container label)
\\CDSESUB1\EVSPROD\ANDA071402\0001

ANDA 74-703Morton Grove (oral syrup) submitted: 3/26/09 - insert, med guide, REMS, container label
\\FDSWA150\NONECTD\N74703\S_006\2009-03-26

ANDA 73-680Silarx (oral syrup) submitted: 3/17/09 - insert, med guide, REMS (missing container label)
\\CDSESUB1\EVSPROD\ANDA073680\0002

ANDA 72-744 Pharmaceutical Associates (oral syrup) submitted: 3/30/09 - med guide and REMS (missing insert and container label) - Not sure if this is electronic. OGD is waiting for their document room to check.

NDA 17-854 Alaven (Reglan Tablets) submitted 3-25-09
Med Guide submission: S-051
The network location is : \\FDSWA150\NONECTD\N17854\S_051\2009-03-25

REMS Submission: S-052
The network location is : \\FDSWA150\NONECTD\N17854\S_052\2009-03-25

NDA 21-793, Alaven (Reglan ODT) submitted 3-25-09
Med Guide submission: S-004
The network location is : \\FDSWA150\NONECTD\N21793\S_004\2009-03-25

REMS Submission: S-005
The network location is : \\FDSWA150\NONECTD\N21793\S_005\2009-03-25

SIGNATURE OF REQUESTOR Kristen Everett/Joyce Korvick	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Kristen Everett

4/3/2009 02:27:52 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Wayne Amchin, DDMAC			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Kristen Everett, SRPM, DGP	
DATE April 6, 2009	IND NO.	NDA NO. multiple- see below	TYPE OF DOCUMENT REMS - MG	DATE OF DOCUMENT March 17, 2009 (earlies submission)
NAME OF DRUG metoclopramide class	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG motility modifiers	DESIRED COMPLETION DATE May 1, 2009

NAME OF FIRM: Alaven Pharma, ANI, Silarx, Morton Grove, Pharmaceutical Associates

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
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- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DGP and OGD request your expertise in the review of the medication guides and REMS documents submitted for the products listed below. EDR links, where available, are provided for the submissions. In addition, package inserts, MGs, and REMS documents will be available in the GI eRoom (Safety folder, REMS/FDAAA Safety Labeling under review, metoclopramide subfolder). The class language that will be harmonized across the medication guides is the Boxed warning, and the Tardive Dyskinesia subsection under Warnings (this language is also provided in the supplement request letter sent to the sponsors). The REMS documents should also be fairly similar in that the REMS goal should be the same; however, sponsors may have different methods of distributing the medication guide. For the package insert, DGP requests only that DDMAC review the class language of the Boxed Warning and warnings section.

ANDA 71-402ANI (oral syrup) submitted: 3/26/09 - insert, med guide, REMS (missing container label)
\\CDSESUB1\EVSPROD\ANDA071402\0001

ANDA 74-703Morton Grove (oral syrup) submitted: 3/26/09 - insert, med guide, REMS, container label
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REMS Submission: S-005
The network location is : \\FDSWA150\NONECTD\N21793\S_005\2009-03-25

SIGNATURE OF REQUESTOR Kristen Everett/Joyce Korvick	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Kristen Everett
4/6/2009 12:05:13 PM

pai Pharmaceutical Associates, Inc.

SUPPLEMENT AMENDMENT

April 8, 2009

SL-010 - AL

Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, MD 20855

RE: PRIOR APPROVAL SUPPLEMENT – ANDA #72-744
Safety Labeling Changes Under 505(o)(4)
Metoclopramide Oral Solution USP, 5 mg/5 mL

Dear Madam/Sir:

Pharmaceutical Associates, Inc is responding to the agency letter dated February 26, 2009, a telephone conversation dated March 19, 2009, a follow-up conversation dated March 26, 2009; and a follow-up conversation dated April 2, 2009 regarding ANDA #72-744 - Metoclopramide Oral Solution USP, 5 mg/5 mL. As outlined in the agency letter, the Prior Approval Supplement – Labeling Supplement includes Safety Labeling Changes Under 505(o)(4).

Enclosed in the submission are FDA Form 356h, a side-by-side comparison of our current/revised package insert (compare.pdf) and draft versions of labeling including the medication guide provided electronically on disk in SPL, Word and PDF formats. The Risk Evaluation and Mitigation Strategy (REMS) was submitted to the agency as a New Supplement For ANDA #72-744 on March 30, 2009 in hardcopy. We are providing the REMS file electronically in the folder marked "other".

If you have any questions or need additional information, please contact Kaye McDonald at (864) 277-7282, extension 3377 or by fax (864) 299-6431.

Best Regards,

Kaye McDonald

Kaye McDonald
Pharmaceutical Associates, Inc
Sr. Director of Regulatory and Product Development

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Fax: (864) 277-8045

Regulatory/Purchasing
201 Delaware Street
Greenville, SC 29605
Phone: (864) 277-7282
Fax: (864) 299-6431

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pai Pharmaceutical Associates, Inc.

April 15, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, MD 20855

SUPPLEMENT AMENDMENT
SL010/RP

RE: AMENDMENT TO SUPPLEMENT - 10
PROPOSED REMS AMENDMENT
ANDA #72-744 - METOCLOPRAMIDE ORAL SOLUTION USP, 5 mg/5 mL

Dear Madam/Sir:

Pharmaceutical Associates, Inc. is responding to the agency letter dated February 26, 2009, a telephone conversation dated March 19, 2009 and follow-up conversations dated March 26, 2009, April 2, 2009, and April 15, 2009 regarding ANDA #72-744 - Metoclopramide Oral Solution USP, 5 mg/5 mL. As outlined in the agency letter, Amendment to Supplement - 10 Proposed REMS Amendment includes Safety Labeling Changes Under 505(o)(4).

Enclosed in the submission is FDA Form 356h. As requested by the agency, The Risk Evaluation and Mitigation Strategy (REMS) and Medication Guide are provided electronically on CD in both word and PDF formats.

If you have any questions or need additional information, please contact Kaye McDonald at (864) 277-7282, extension 3377 or by fax (864) 299-6431.

Best Regards,

Kaye McDonald

Kaye McDonald
Pharmaceutical Associates, Inc.
Sr. Director of Regulatory and Product Development

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pai Pharmaceutical Associates, Inc.

May 12, 2009

SUPPLEMENT AMENDMENT
SL- 010-AL

Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, MD 20855

RE: AMENDMENT TO SUPPLEMENT - 10
PRIOR APPROVAL SUPPLEMENT
ANDA #72-744 - METOCLOPRAMIDE ORAL SOLUTION USP, 5 mg/5 mL

Dear Madam/Sir:

Pharmaceutical Associates, Inc. is responding to the email dated May 6, 2009 from the agency regarding ANDA #72-744 - Metoclopramide Oral Solution USP, 5 mg/5 mL package insert and medication guide changes.

Enclosed in the submission is FDA Form 356h. As requested by the agency, the package insert with the medication guide incorporated is provided as a Word version (with track changes) electronically on CD.

If you have any questions or need additional information, please contact Kaye McDonald at (864) 277-7282, extension 3377 or by fax (864) 299-6431.

Best Regards,

Kaye McDonald

Kaye McDonald
Pharmaceutical Associates, Inc.
Sr. Director of Regulatory and Product Development

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pai Pharmaceutical Associates, Inc.

June 16, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, MD 20855

SUPPLEMENT AMENDMENT

SL - 010 - AL

RE: AMENDMENT TO SUPPLEMENT - 10
ANDA #72-744 - METOCLOPRAMIDE ORAL SOLUTION USP, 5 mg/5 mL

Dear Madam/Sir:

Pharmaceutical Associates, Inc. is responding to the email dated June 8, 2009 from the agency regarding ANDA #72-744 - Metoclopramide Oral Solution USP, 5 mg/5 mL medication guide changes.

Enclosed in the submission is FDA Form 356h. As requested by the agency, the package insert with the medication guide incorporated is provided as a Word version (with track changes) electronically on CD.

If you have any questions or need additional information, please contact Kaye McDonald at (864) 277-7282, extension 3377 or by fax (864) 299-6431.

Best Regards,

Kaye McDonald

Kaye McDonald
Pharmaceutical Associates, Inc.
Sr. Director of Regulatory and Product Development

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pai Pharmaceutical Associates, Inc.

June 30, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, MD 20855

SUPPLEMENT AMENDMENT
SL-010-AL

RE: AMENDMENT TO SUPPLEMENT - 10
ANDA #72-744 - METOCLOPRAMIDE ORAL SOLUTION USP, 5 mg/5 mL

Dear Madam/Sir:

Pharmaceutical Associates, Inc. is responding to the email dated June 24, 2009 from the agency regarding ANDA #72-744 - Metoclopramide Oral Solution USP, 5 mg/5 mL package insert and medication guide changes.

Enclosed in the submission is FDA Form 356h. As requested by the agency, final printed labeling is provided electronically on CD as PDF documents for the package insert and medication guide. In addition, electronically on CD are the final word versions with track changes removed for the package insert and medication guide.

If you have any questions or need additional information, please contact Kaye McDonald at (864) 277-7282, extension 3377 or by fax (864) 299-6431.

Best Regards,

Kaye McDonald

Kaye McDonald
Pharmaceutical Associates, Inc.
Sr. Director of Regulatory and Product Development

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

ANDA 72-744/S-011

INFORMATION REQUEST LETTER

Pharmaceutical Associates, Inc.
Attention: Kaye McDonald
Sr. Director of Regulatory and Product Development
201 Delaware Street
Greenville, SC 29605

Dear Madam:

Please refer to your supplemental new drug application ANDA 72-744 for Metoclopramide Oral Solution USP, 5 mg/5 mL, which was approved on May 28, 1991.

We also refer to your submissions dated March 30, 2009.

We are reviewing the REMS section of your submissions and have the following comments and information requests. We request a prompt written response by July 20, 2009 in order to continue our evaluation of your REMS.

Goal of REMS

1. Revise your REMS goal as follows to be consistent with REMS goal for all metoclopramide products:

   > The goal of this REMS is to minimize the risk of tardive dyskinesia associated with long-term use of Metoclopramide Oral Solution.

Medication Guide

2. Your proposed REMS does not provide enough detail to determine whether your Medication Guide distribution procedure is acceptable. Revise and resubmit a Medication Guide distribution procedure that ensures sufficient numbers of Medications Guides will be provided with the product such that each patient will receive a printed, hard-copy of the approved Medication Guide. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

- A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
- A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

3. We remind you of the requirement to comply with 21 CFR 208.24. A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use): "Dispense the enclosed Medication Guide to each patient." or "Dispense the accompanying Medication Guide to each patient."

Please see appended REMS proposal for additional track changes corresponding to comments in this review. Submit the revised REMS with appended materials and documents by **July 20, 2009**. It is preferable that the entire REMS and appended materials be submitted as a single WORD document. If certain documents are only in PDF format, they may be submitted as such, but the preference is a single WORD document.

If you have any questions, please call Sarah Park, Labeling Reviewer, at (240) 276-8995.

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Following this page, 2 pages withheld in full - (b)(4) draft labeling.

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

/s/

Koung Lee
7/14/2009 12:16:52 PM
For Wm Peter Rickman

pai Pharmaceutical Associates, Inc.

August 3, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, MD 20855

SD-66

Changed to New supplement SD-11 REMS Sel.

RE: AMENDMENT TO SUPPLEMENT - 10
ANDA #72-744 - METOCLOPRAMIDE ORAL SOLUTION USP, 5 mg/5 mL

Dear Madam/Sir:

Pharmaceutical Associates, Inc. is responding to the agency letter dated June 14, 2009 from the agency regarding ANDA #72-744 - Metoclopramide Oral Solution USP, 5 mg/5 mL.

Enclosed in the submission is FDA Form 356h. As requested by the agency, the REMS and approved Medication Guide are included on CD as single word documents with track changes.

Please note: A typographical error was found on the approved Medication Guide (R05/09) approved by the agency on July 2, 2009. The word "methylparaben" was inadvertently spelled incorrect; the error was corrected and noted as a change. The revised Medication Guide will be sent to the agency as a separate submission labeled Changes Being Effected – 0 (CBE-0) noting the error.

If you have any questions or need additional information, please contact Kaye McDonald at (864) 277-7282, extension 3377 or by fax (864) 299-6431.

Best Regards,

Kaye McDonald

Kaye McDonald
Pharmaceutical Associates, Inc.
Sr. Director of Regulatory and Product Development

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