CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 72-744/S-010

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

Sponsor: Pharmaceutical Associates, Inc.

Approval Date: July 02, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

ANDA 72-744/S-010

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 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Metoclopramide Oral Solution USP, 5 mg/5 mL.

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

Reference is also made to our letter dated February 26, 2009, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Metoclopramide Oral Solution USP, 5 mg/5 mL. This information pertains to the risk of tardive dyskinesia.

This supplemental new drug application provides for revisions to the labeling for Metoclopramide Oral Solution USP, 5 mg/5 mL, consistent with our February 26, 2009, letter and correspondences between FDA and Pharmaceutical Associates dated May 6, June 8, and June 24, 2009.

We have completed our review of this supplemental application, as amended, and it is approved.

Your approved Medication Guide will become part of the Risk Evaluation and Mitigation Strategy (REMS) in pending supplement ANDA 72-744/S-011.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling (21 CFR 314.50(1)) in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the attached labeling and Medication Guide.

Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **"SPL for approved ANDA 72-744/S-010."** In addition, within 21 days of the date of this letter, amend any pending supplement for this ANDA.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

Marketing the product with FPL that is not identical to the approved labeling and in the required format may render the product misbranded and an unapproved generic drug.

Please note that:

- this Medication Guide must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling [21 CFR 201.57(c)(18) or 21 CFR 201.80(f)(2)];

- you are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208.24];

- the final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text; and

- you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided [21 CFR 208.24(d)]

LETTER TO HEALTH CARE 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

We remind you that you must comply with reporting requirements for an approved ANDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact 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: Package Insert and Medication Guide

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

/s/

Gary Buehler

7/2/2009 04:45:56 PM

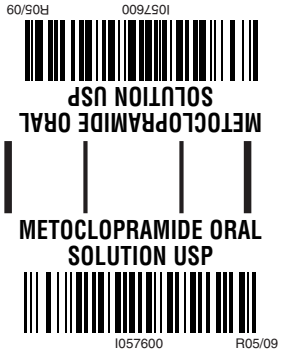
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-010

LABELING

ACTUAL SIZE



METOCLOPRAMIDE ORAL SOLUTION USP

Rx ONLY

WARNING: TARDIVE DYSKINESIA

Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose.

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

Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia. *See* WARNINGS.

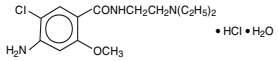
DESCRIPTION

Metoclopramide Oral Solution USP is an orange-colored, berry-citrus flavored liquid for oral administration.

Each 5 mL (teaspoonful) for oral administration contains: Metoclopramide base (as he monohyd ochloride monohydrate) 5 mg.

Inactive ingredients: Citric acid, FD&C Yellow No. 6 (Sunset Yellow), flavoring, glycerin, me hylparaben, p opylparaben, purified water, and sorbitol solution.

Metoclopramide hyd ochloride is a white, crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5-chlo o-N-[2-(die hylamino)e hyl]-2-me hoxy benzamide monohyd ochloride monohydrate. Its molecular formula is: $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$. Molecular weight: 354.3. Its structural formula is:



CLINICAL PHARMACOLOGY

Metoclopramide stimulates motility of the upper gast ointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to he action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

Metoclopramide increases he tone and amplitude of gastric (especially antral) contractions, relaxes he pyloric sphincter and he duodenal bulb, and increases peristalsis of he duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases he resting tone of the lower esophageal sphincter. It has little, if any effect on the motility of the colon or gallbladder.

In patients with gast oesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide p oduce dose-related increases in LESP. Effects begin at about 5 mg and increase th ough 20 mg (he largest dose tested). The increase in LESP f om a 5 mg dose lasts about 45 minutes and hat of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed wi h single oral doses of 10 mg.

The antiemetic p operties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine p oduces nausea and vomiting by stimulation of he medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of he CTZ by agents like L-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Like he phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide p oduces sedation and may p oduce extrapyramidal reactions, al hough hese are comparatively rare (See **WARNINGS**). Metoclopramide inhibits he central and peripheral effects of apomorphine, induces release of p olactin and causes a transient increase in circulating aldoste one levels, which may be associated wi h transient fluid retention.

The onset of pharmacological action of metoclopramide is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 30 to 60 minutes following an oral dose; pharmacological effects persist for 1 to 2 hours.

Pharmacokinetics

Metoclopramide is rapidly and well absorbed. Relative to an intravenous dose of 20 mg, the absolute oral bioavailability of metoclopramide is 80% ± 15.5% as demonstrated in a c ossover study of 18 subjects. Peak plasma concentrations occur at about 1 to 2 hours after a single oral dose. Similar time to peak is observed after individual doses at steady state.

In a single dose study of 12 subjects, he area under the drug concentration-time curve increased linearly wi h doses f om 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and he elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5 to 6 hours. Linear kinetic p ocesses adequately describe the absorption and elimination of metoclopramide.

App oximately 85% of the radioactivity of an orally administered dose appears in the urine wi hin 72 hours. Of the 85% eliminated in he urine, about half is present as free or conjugated metoclopramide.

The drug is not extensively bound to plasma p oteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to he tissues.

ACTUAL SIZE

Renal impairment affects he clearance of metoclopramide. In a study wi h patients wi h varying degrees of renal impairment, a reduction in creatinine clearance was correlated wi h a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life. The kinetics of metoclopramide in he presence of renal impairment remained linear however. The reduction in clearance as a result of renal impairment suggests that adjustment downward of maintenance dosage should be done to avoid drug accumulation.

Adult Pharmacokinetic Data

Parameter	Value
Vd (L/kg)	~3.5
Plasma P otein Binding	~30%
$t_{1/2}$ (hr)	5 to 6
Oral Bioavailability	80%±15.5%

In pediatric patients, he pharmacodynamics of metoclopramide following oral and intravenous administration are highly variable and a concentration-effect relationship has not been established.

There are insufficient reliable data to conclude whe her the pharmacokinetics of metoclopramide in adults and he pediatric population are similar. Al hough there are insufficient data to support he efficacy of metoclopramide in pediatric patients with symptomatic gast oesophageal reflux (GER) or cancer chemo herapy-related nausea and vomiting, its pharmacokinetics have been studied in hese patient populations.

In an open-label study, six pediatric patients (age range, 3.5 weeks to 5.4 months) with GER received metoclopramide 0.15 mg/kg oral solution every 6 hours for 10 doses. The mean peak plasma concentration of metoclopramide after the ten h dose was 2-fold (56.8 μg/L) higher compared to that observed after he first dose (29 μg/L) indicating drug accumulation wi h repeated dosing. After he ten h dose, the mean time to reach peak concentrations (2.2 hr), half-life (4.1 hr), clearance (0.67 L/h/kg), and volume of distribution (4.4 L/kg) of metoclopramide were similar to hose observed after the first dose. In he youngest patient (age, 3.5 weeks), metoclopramide half-life after the first and he ten h dose (23.1 and 10.3 hr, respectively) was significantly longer compared to o her infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at bir h.

Single intravenous doses of metoclopramide 0.22 to 0.46 mg/kg (mean, 0.35 mg/kg) were administered over 5 minutes to 9 pediatric cancer patients receiving chemo herapy (mean age, 11.7 years; range, 7 to 14 yr) for p ophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time ze o ranged f om 65 to 395 mcg/L (mean, 152 mcg/L). The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.4 hr (range, 1.7 to 8.3 hr), 0.56 L/h/kg (range, 0.12 to 1.20 L/h/kg), and 3 L/kg (range, 1 to 4.8 L/kg), respectively.

In another study, nine pediatric cancer patients (age range, 1 to 9 yr) received 4 to 5 intravenous infusions (over 30 minutes) of metoclopramide at a dose of 2 mg/kg to cont ol emesis. After the last dose, he peak serum concentrations of metoclopramide ranged f om 1060 to 5680 mcg/L. The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5 hr (range, 2 to 12.5 hr), 0.37 L/h/kg (range, 0.1 to 1.24 L/h/kg), and 1.93 L/kg (range, 0.95 to 5.5 L/kg), respectively.

INDICATIONS AND USAGE

The use of Metoclopramide Oral Solution is recommended for adults only. Therapy should not exceed 12 weeks in duration.

Symptomatic Gastroesophageal Reflux

Metoclopramide Oral Solution USP is indicated as short-term (4 to 12 weeks) herapy for adults wi h symptomatic, documented gast oesophageal reflux who fail to respond to conventional herapy.

The principal effect of metoclopramide is on symptoms of postprandial and daytime heartbu n wi h less observed effect on noctu nal symptoms. If symptoms are confined to particular situations, such as following he evening meal, use of metoclopramide as single doses prior to the p ovocative situation should be considered, ra her han using he drug h oughout the day. Healing of esophageal ulcers and e osions has been endoscopically demonstrated at he end of a 12-week trial using doses of 15 mg q.i.d. As there is no documented correlation between symptoms and healing of esophageal lesions, patients wi h documented lesions should be monitored endoscopically.

Diabetic Gastroparesis (diabetic gastric stasis) Metoclopramide is indicated for he relief of symptoms associated wi h acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartbu n, persistent fullness after meals, and anorexia) appear to respond to metoclopramide wi hin different time intervals. Significant relief of nausea occurs early and continues to imp ove over a hree-week period. Relief of vomiting and anorexia may precede he relief of abdominal fullness by one week or more.

CONTRAINDICATIONS

Metoclopramide should not be used whenever stimulation of gast ointestinal motility might be dange ous, e.g., in he presence of gast ointestinal hemor hage, mechanical obstruction, or perforation.

Metoclopramide is contraindicated in patients wi h pheoch omocytoma because the drug may cause a hypertensive crisis, p obably due to release of catecholamines f om the tumor. Such hypertensive crises may be cont olled by phentolamine.

Metoclopramide is contraindicated in patients wi h known sensitivity or intolerance to he drug.

ACTUAL SIZE

Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

WARNINGS

Mental depression has occurred in patients with and wi hout prior history of depression. Symptoms have ranged f om mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients wi h a prior history of depression only if he expected benefits outweigh the potential risks.

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in app oximately 1 in 500 patients treated with he usual adult dosages of 30 to 40 mg/day of metoclopramide. These usually are seen during the first 24 to 48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less han 30 years of age and are even more frequent at he higher doses. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, hy hmic p otrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm. If hese symptoms should occur, 50 mg of diphenhydramine hyd ochloride injection should be given intramuscularly, and hey usually will subside. Benzt opine mesylate, 1 to 2 mg intramuscularly, may also be used to reverse hese reactions.

Parkinsonian-like symptoms have occurred, more commonly within he first 6 mon hs after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside wi hin 2 to 3 mon hs following discontinuance of metoclopramide. Patients wi h pre-existing Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

Tardive Dyskinesia

Tardive Dyskinesia (see Boxed Warnings)

Treatment wi h metoclopramide can cause tardive dyskinesia (TD), a potentially irreversible and disfiguring disorder characterized by involuntary movements of he face, tongue, or extremities. Al hough he risk of TD wi h metoclopramide has not been extensively studied, one published study reported a TD prevalence of 20% among patients treated for at least 12 weeks. Treatment wi h metoclopramide for longer than 12 weeks should be avoided in all but rare cases where herapeutic benefit is hought to outweigh the risk of developing TD.

Although he risk of developing TD in he general population may be increased among the elderly, women, and diabetics, it is not possible to predict which patients will develop metoclopramide-induced TD. Bo h he risk of developing TD and the likelihood hat TD will become irreversible increase wi h duration of treatment and total cumulative dose.

Metoclopramide should be discontinued in patients who develop signs or symptoms of TD. There is no known effective treatment for established cases of TD, al hough in some patients, TD may remit, partially or completely, wi hin several weeks to mon hs after metoclopramide is withdrawn.

Metoclopramide itself may suppress, or partially suppress, he signs of TD, hereby masking he underlying disease process. The effect of his symptomatic suppression upon he long-term course of TD is unknown. Therefore, metoclopramide should not be used for he symptomatic cont ol of TD.

Neuroleptic Malignant Syndrome

There have been rare reports of an uncommon, but potentially fatal symptom complex sometimes referred to as Neu oleptic Malignant Synd ome (NMS) associated wi h metoclopramide. Clinical manifestations of NMS include hyper hermia, muscle rigidity, altered consciousness, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac ar hy hmias).

The diagnostic evaluation of patients wi h his synd ome is complicated. In arriving at a diagnosis, it is important to identify cases where he clinical presentation includes bo h serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in he differential diagnosis include central anticholinergic toxicity, heat st oke, malignant hyperthermia, drug fever and primary central nervous system (CNS) pa hology.

The management of NMS should include 1) immediate discontinuation of metoclopramide and o her drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical p oblems for which specific treatments are available. B omocriptine and dant olene sodium have been used in treatment of NMS, but their effectiveness have not been established (see **ADVERSE REACTIONS**).

PRECAUTIONS

General

In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, caution should be exercised when metoclopramide is used in patients wi h hypertension.

Because metoclopramide p oduces a transient increase in plasma aldoste one, certain patients, especially those wi h cir hosis or congestive heart failure, may be at risk of developing fluid retention and volume overload. If hese side effects occur at any time during metoclopramide therapy, the drug should be discontinued.

Adverse reactions, especially hose involving he nervous system, may occur after stopping he use of metoclopramide. A small number of patients may

ACTUAL SIZE

experience a wi hdrawal period after stopping metoclopramide hat could include dizziness, nervousness, and/or headaches.

Information for Patients

The use of metoclopramide oral solution is recommended for adults only. Metoclopramide may impair he mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be cautioned accordingly.

Drug Interactions

The effects of metoclopramide on gast ointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given wi h alcohol, sedatives, hypnotics, narcotics or tranquilizers.

The finding that metoclopramide releases catecholamines in patients wi h essential hypertension suggests hat it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

Absorption of drugs f om he stomach may be diminished (e.g., digoxin) by metoclopramide, whereas he rate and/or extent of absorption of drugs f om the small bowel may be increased (e.g., acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

Gast oparesis (gastric stasis) may be responsible for poor diabetic cont ol in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because he action of metoclopramide will influence the delivery of food to he intestines and hus the rate of absorption, insulin dosage or timing of dosage may require adjustment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 77-week study was conducted in rats with oral doses up to about 40 times the maximum recommended human daily dose. Metoclopramide elevates p olactin levels and the elevation persists during ch onic administration. Tissue culture experiments indicate that app oximately one- hird of human breast cancers are p olactin-dependent *in vitro*, a factor of potential importance if he prescription of metoclopramide is contemplated in a patient wi h previously detected breast cancer. Although disturbances such as galactor- hea, amenor hea, gynecomastia, and impotence have been reported wi h p olactin-elevating drugs, he clinical significance of elevated serum p olactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after ch onic administration of p olactin-stimulating neu oleptic drugs and metoclopramide. Nei her clinical studies nor epidemiologic studies conducted to date, however, have shown an association between ch onic administration of hese drugs and mammary tumorigenesis; he available evidence is too limited to be conclusive at this time.

An Ames mutagenicity test performed on metoclopramide was negative.

Pregnancy Category B

Rep oduction studies performed in rats, mice, and rabbits by he I.V., I.M., S.C. and oral outes at maximum levels ranging f om 12 to 250 times he human dose have demonstrated no impairment of fertility or significant harm to the fetus due to metoclopramide. There are, however, no adequate and well-cont olled studies in pregnant women. Because animal rep oduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mo her.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established (see **OVERDOSAGE**).

Care should be exercised in administering metoclopramide to neonates since p olonged clearance may p oduce excessive serum concentrations (see **CLINICAL PHARMACOLOGY — Pharmacokinetics**). In addition, neonates have reduced levels of NADH-cytoch ome b_5 reductase, which, in combination with he aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia (see **OVERDOSAGE**).

The safety p ofile of metoclopramide in adults cannot be extrapolated to pediatric patients. Dystonias and o her extrapyramidal reactions associated wi h metoclopramide are more common in the pediatric population than in adults. (See **WARNINGS** and **ADVERSE REACTIONS — Extrapyramidal Reactions**.)

Geriatric Use

Clinical studies of metoclopramide did not include sufficient numbers of subjects aged 65 and over to determine whe her elderly subjects respond differently f om younger subjects.

The risk of developing parkinsonian-like side effects increases wi h ascending dose. Geriatric patients should receive he lowest dose of metoclopramide that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving metoclopramide, metoclopramide should generally be discontinued before initiating any specific antiparkinsonian agents (see **WARNINGS** and **DOSAGE AND ADMINISTRATION - For the Relief of Symptomatic Gastroesophageal Reflux**).

The elderly may be at greater risk for tardive dyskinesia (see **WARNINGS - Tardive Dyskinesia**).

Sedation has been reported in metoclopramide users. Sedation may cause confusion and manifest as over-sedation in he elderly (see **CLINICAL PHARMACOLOGY, PRECAUTIONS - Information for Patients** and **ADVERSE REACTIONS - CNS Effects**).

ACTUAL SIZE

Metoclopramide is known to be substantially excreted by the kidney, and he risk of toxic reactions to his drug may be greater in patients wi h impaired renal function (see **DOSAGE AND ADMINISTRATION - USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT**).

For hese reasons, dose selection for an elderly patient should be cautious, usually starting at he low end of he dosing range, reflecting the greater frequency of decreased renal functions, concomitant disease, or other drug therapy in the elderly (see **DOSAGE AND ADMINISTRATION - For the Relief of Symptomatic Gastroesophageal Reflux** and **USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT**).

Other Special Populations

Patients wi h NADH-cytoch ome b_5 reductase deficiency are at an increased risk of developing me hemoglobinemia and/or sul hemoglobinemia when metoclopramide is administered. In patients wi h G6PD deficiency who experience metoclopramide-induced me hemoglobinemia, me hylene blue treatment is not recommended (see **OVERDOSAGE**).

ADVERSE REACTIONS

In general, the incidence of adverse reactions correlates wi h the dose and duration of metoclopramide administration. The following reactions have been reported, al hough in most instances, data do not permit an estimate of frequency.

CNS Effects

Restlessness, d owsiness, fatigue and lassitude occur in app oximately 10% of patients receiving the most commonly prescribed dosage of 10 mg q.i.d. (see **PRECAUTIONS**). Insomnia, headache, confusion, dizziness or mental depression with suicidal ideation (see **WARNINGS**) occur less frequently. The incidence of d owsiness is greater at higher doses. There are isolated reports of convulsive seizures without clearcut relationship to metoclopramide. Rarely, hallucinations have been reported.

Extrapyramidal Reactions (EPS)

Acute dystonic reactions, the most common type of EPS associated wi h metoclopramide, occur in app oximately 0.2% of patients (1 in 500) treated wi h 30 to 40 mg of metoclopramide per day.

Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, hythmic p otrusion of tongue, bulbar type of speech, trismus, opis hotonus (tetanus-like reactions) and rarely, stridor and dyspnea, possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine (see **WARNINGS**).

Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies (see **WARNINGS**).

Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth, or jaw, and sometimes by involuntary movements of the trunk and/or extremities; movements may be choreoathetotic in appearance (see **WARNINGS**).

Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing and foot-tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

Neuroleptic Malignant Syndrome

Rare occurrences of neu oleptic malignant synd ome (NMS) have been reported. This potentially fatal synd ome is comprised of he symptom complex of hyperthermia, altered consciousness, muscular rigidity, and autonomic dysfunction (see **WARNINGS**).

Endocrine Disturbances

Galactor hea, amenor hea, gynecomastia, impotence secondary to hyper-p olactinemia (see **PRECAUTIONS**). Fluid retention secondary to transient elevation of aldoste one (see **CLINICAL PHARMACOLOGY**).

Cardiovascular

Hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention, acute congestive heart failure and possible AV block (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Gastrointestinal

Nausea and bowel disturbances, primarily diar hea.

Hepatic

Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered wi h o her drugs wi h known hepatotoxic potential.

Renal

Urinary frequency and incontinence.

Hematologic

A few cases of neut openia, leukopenia, or agranulocytosis, generally without clearcut relationship to metoclopramide. Me hemoglobinemia, in adults and especially with overdosage in neonates (see **OVERDOSAGE**).
Sul hemoglobinemia in adults.

Allergic Reactions

A few cases of rash, urticaria, or b onchospasm, especially in patients wi h a history of asthma. Rarely, angioneu otic edema, including glossal or laryngeal edema.

Miscellaneous

Visual disturbances. Porphyria.

OVERDOSAGE

Symptoms of overdosage may include d owsiness, disorientation and extrapyramidal reactions. Anticholinergic or antiparkinson drugs or anti-histamines wi h anticholinergic p operties may be helpful in cont olling he extrapyramidal reactions. Symptoms are self-limiting and usually disappear wi hin 24 hours.

ACTUAL SIZE

Hemodialysis removes relatively little metoclopramide, p obably because of the small amount of he drug in blood relative to tissues. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of drug. It is unlikely that dosage would need to be adjusted to compensate for losses th ough dialysis. Dialysis is not likely to be an effective me hod of drug removal in overdose situations.

Unintentional overdose due to misadministration has been reported in infants and children wi h he use of metoclopramide oral solution. While here was no consistent patte n to the reports associated w th hese overdoses, events included seizures, extrapyramidal reactions, and le hargy.

Me hemoglobinemia has occurred in premature and full-term neonates who were given overdoses of metoclopramide (1 to 4 mg/kg/day orally, intramuscularly or intravenously for 1 to 3 or more days). Methemoglobinemia can be reversed by he intravenous administration of me hylene blue. However, me hylene blue may cause hemolytic anemia in patients wi h G6PD deficiency, which may be fatal. (see **PRECAUTIONS - Other Special Populations**).

DOSAGE AND ADMINISTRATION

Therapy with metoclopramide oral solution should not exceed 12 weeks in duration.

For the Relief of Symptomatic Gastroesophageal Reflux

Administer f om 10 mg to 15 mg Metoclopramide Oral Solution USP (orally) up to q.i d. 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response (see **CLINICAL PHARMACOLOGY** and **INDICATIONS AND USAGE**). If symptoms occur only intermittently or at specific times of he day, use of metoclopramide in single doses up to 20 mg prior to he p ovoking situation may be preferred ra her than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the herapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

Experience with esophageal e osions and ulcerations is limited, but healing has thus far been documented in one controlled trial using q.i d. herapy at 15 mg/dose, and his regimen should be used when lesions are present, so long as it is tolerated (see **ADVERSE REACTIONS**). Because of the poor correlation between symptoms and endoscopic appearance of the esophagus, therapy directed at esophageal lesions is best guided by endoscopic evaluation.

Therapy longer han 12 weeks has not been evaluated and cannot be recommended.

For the Relief of Symptoms Associated with Diabetic Gastroparesis (diabetic gastric stasis) Administer 10 mg of metoclopramide 30 minutes before each meal and at bedtime for two to eight weeks, depending upon response and he like ihood of continued well-being upon drug discontinuation.

The initial oute of administration should be determined by he severity of the presenting symptoms. If only he earliest manifestations of diabetic gastric stasis are present, oral administration of metoclopramide may be initiated. However, if severe symptoms are present, herapy should begin wi h metoclopramide injection (consult labeling of he injection prior to initiating parenteral administration).

Administration of he metoclopramide injection up to 10 days may be required before symptoms subside, at which time oral administration may be instituted. Since diabetic gastric stasis is frequently recurrent, metoclopramide therapy should be reinstituted at he earliest manifestation.

USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

Since metoclopramide is excreted principally h ough he kidneys, in those patients whose creatinine clearance is below 40 mL/min, herapy should be initiated at app oximately one-half he recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as app opriate.

See **OVERDOSAGE** section for information regarding dialysis.

Metoclopramide undergoes minimal hepatic metabolism, except for simple conjugation. Its safe use has been described in patients wi h advanced liver disease whose renal function was normal.

HOW SUPPLIED

Metoclopramide Oral Solution USP, 5 mg metoclopramide base (as he monohyd ochloride monohydrate) per 5 mL (teaspoonful) is available as an orange-colored, berry-citrus flavored, sugar-free solution and is supplied in the following oral dosage forms: NDC 0121-1576-10 (Unit dose cups of 10 mg/10 mL, 10 unit dose cups per tray, 10 trays per case) and NDC 0121-0576-16 (16 fl oz bottles).

Dispense in a tight, light-resistant container.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Manufactured By:

www.paipharma.com

R05/09

ACTUAL SIZE

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.

ACTUAL SIZE

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.

ACTUAL SIZE

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 about know 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

ACTUAL SIZE

- 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 68°F to 77°F (20°C to 25°C).
- 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.

pai Pharmaceutical Associates, Inc.
Greenville, SC 29605
www.paipharma.com

R05/09

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

NDC 0121-0576-16
NSN 6505-01-212-8750

Metoclopramide Oral Solution USP

5 mg/5 mL*

*Each 5 mL (1 teaspoonful) contains:
Metoclopramide ..... 5 mg
(present as the hydrochloride)

FOR DOSAGE AND OTHER PRESCRIBING INFORMATION, SEE ACCOMPANYING PRODUCT LITERATURE.

PHARMACIST: Dispense the important Medication Guide about the risks of Tardive Dyskinesia with the drug product. The guide is included with the accompanying product literature.

BULK CONTAINER - NOT FOR HOUSEHOLD DISPENSING

Rx ONLY

16 fl oz (473 mL)

pai Pharmaceutical Associates, Inc.
Greenville, SC 29605

Store at controlled room temperature, between 20°-25°C (68°-77°F). [See USP]
Dispense in a tight, light-resistant container.

NO VARNISH

LOT:
EXP.

L05761600

R04/09

N 3 0121-0576-16 4

ACTUAL SIZE

NDC 0121-0576-16
NSN 6505-01-212-8750

Metoclopramide Oral Solution USP

5 mg/5 mL*

*Each 5 mL (1 teaspoonful) contains:
Metoclopramide ..... 5 mg
(present as the hydrochloride)

FOR DOSAGE AND OTHER PRESCRIBING INFORMATION, SEE ACCOMPANYING PRODUCT LITERATURE.

PHARMACIST: Dispense the important Medication Guide about the risks of Tardive Dyskinesia with the drug product. The guide is included with the accompanying product literature.

BULK CONTAINER - NOT FOR HOUSEHOLD DISPENSING

Rx ONLY

16 fl oz (473 mL)

pai Pharmaceutical Associates, Inc.
Greenville, SC 29605

Store at controlled room temperature, between 20°-25°C (68°-77°F). [See USP]
Dispense in a tight, light-resistant container.

NO VARNISH

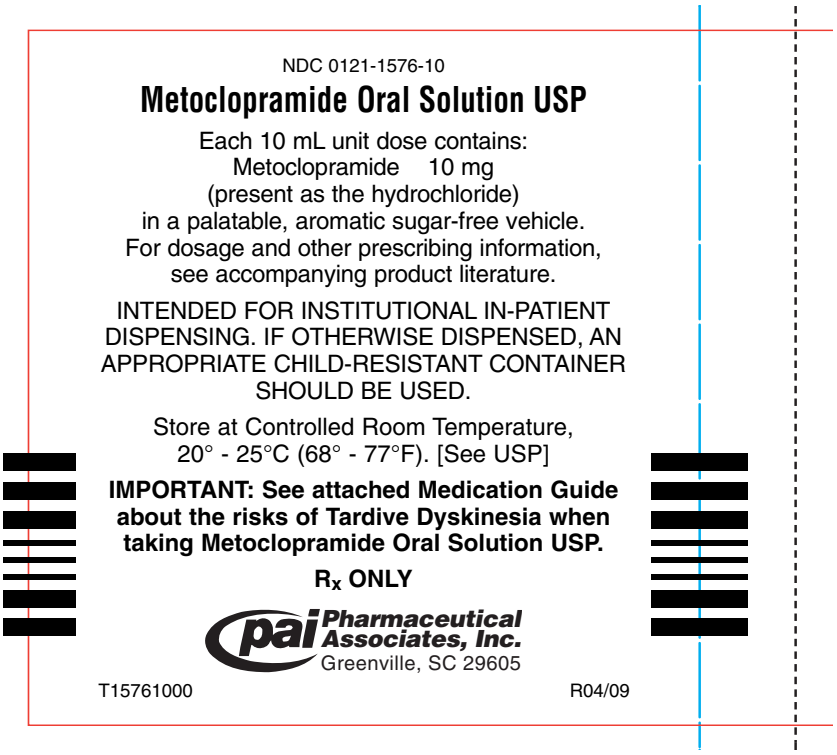
LOT:
EXP.

L05761600

R04/09

N 3 0121-0576-16 4

ACTUAL SIZE 100%



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-010

LABELING REVIEW(S)

Labeling Review Branch

Division of Labeling and Program Support
Office of Generic Drugs

Labeling Supplement Review

Application Number: 72-744/S-010

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	Prior Approval Supplement submission: Hard copies of medication guide and REMS
April 8, 2009	E-submission: Proposed insert, medication guide, bottle label; and unit dose carton labeling in final print; proposed REMS
April 15, 2009	E-submission: medication guide in draft; REMS
May 12, 2009	E-submission: revised insert and medication guide in draft
June 16, 2009	E-submission: revised insert and medication guide in draft
June 30, 2009	E-submission: revised insert and medication guide in final print

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 products 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).

2. This supplemental application provides for revisions to the labeling for Metoclopramide Oral Solution USP, 5 mg/5 mL consistent with our February 26, 2009, letter and correspondences between FDA and Pharmaceutical Associates, Inc. dated May 6, June 8, and June 24, 2009.

3. RLD is ANDA 74-703 Metoclopramide Oral Solution, by Morton Grove Pharmaceuticals Inc.
   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

1. Professional Insert was reviewed by Dr. Christopher Leptak, Medical Officer, of the Division of Gastroenterology Products, and found acceptable.

2. The Medication Guide was reviewed by Dr. Tamara Johnson, Medical Officer, of the Division of Gastroenterology Products and found acceptable.

3. REMS was consulted to OSE and reviewed by Mary Dempsey, Risk Management Program Coordinator (DRISK). The REMS review signed on June 24, 2009 recommends comments to be communicated to the firm. The REMS will not be approved at this time.

4. Unit dose carton:
   - The carton contains 10 x 10 mL unit-dose containers.
   - The carton states that the product is intended for institutional in-patient dispensing.
   - The firm added the statement "**IMPORTANT: See attached Medication Guide about the risks of Tardive Dyskinesia when taking Metoclopramide Oral Solution USP**" to the principal display panel.
   - The firm is asked to add the expression of strength and expression of quantity to the carton labeling.

5. CONTAINER (16 fl oz):
   - The container states that the packaging is a bulk container, not intended for household dispensing.
   - The firm added the statement "**PHARMACIST:** Dispense the important Medication Guide about the risks of Tardive Dyskinesia with the drug product. The guide is included with the accompanying product literature." to the principal display panel.
   - Firm is asked to remove "BULK CONTAINER".
   - Firm is asked to revise the medication guide statement to read "**PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED WITH PRODUCT**" and relocate the Medication Guide statement to appear below the expression of strength.

Recommendation

The submitted labels and labeling are acceptable with comments.

CONTAINER (16 fl oz bottles): Satisfactory in final print as submitted in the April 8, 2009 e-submission.

CARTON (10 x 10 mL unit dose containers): Satisfactory in final print as submitted in the April 8, 2009 e-submission.

INSERT: Satisfactory in final print as submitted in the June 30, 2009 e-submission.

Medication Guide: Satisfactory in final print as submitted in the June 30, 2009 e-submission.

COMMENTS TO FIRM:

1. CONTAINER:

    a. Please revise the Medication Guide statement to read as follows: "**PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED WITH PRODUCT**"

    b. Please relocate the Medication Guide statement to appear between the expression of strength and the "*Each 5 mL…" statement.

    c. Please delete "BULK CONTAINER". You may retain "NOT FOR HOUSEHOLD DISPENSING".

2. CARTON:

    a. Please add the expression of strength.

    b. Please add the erepression of quantity.

{see appended electronic signature}

Sarah Park
Labeling Reviewer

Supervisory Comment/Concurrence:

{see appended electronic signature}

Koung Lee
Team Leader

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
7/2/2009 04:42:00 PM
LABELING REVIEWER

Koung Lee
7/2/2009 04:55:57 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-010

MEDICAL REVIEW(S)

DIVISION OF GASTROENTEROLOGY PRODUCTS
MEDICAL OFFICER'S REVIEW

FDAAA SAFETY REVIEW OF MEDICATION GUIDES FOR METOCLOPRAMIDE REFERENCE LISTED DRUGS

Drug Product/Formulation/ Sponsor Name/ NDA or ANDA #	Indications:	Date of Submission	FDAAA Action Date
Reglan Tablets (Alaven Pharmaceuticals) NDA 017854	• Diabetic Gastroparesis (Diabetic Gastric Stasis) • Symptomatic Gastroesophageal Reflux Disease (GERD)	March 25, 2009	June 24, 2009
Reglan Oral Disintegrating Tablets (Alaven Pharmaceuticals) NDA 021793		March 25, 2009	June 24, 2009
Metoclopramide oral solution (Morton Grove Pharmaceuticals) ANDA 074703		March 27, 2009	June 25, 2009
Metoclopramide oral solution (Silarx Pharmaceuticals Inc) ANDA 073680		March 17, 2009	June 17, 2009
Metoclopramide oral solution (Pharmaceutical Associates Inc) ANDA 072744		March 31, 2009	June 29, 2009
Metoclopramide oral solution (ANI Pharmaceuticals Inc) ANDA 071402		March 27, 2009	June 25, 2009
Reglan Injection (Baxter Healthcare Corp) NDA 017862	• 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	March 26, 2009	June 25, 2009

Review completed: **June 29, 2009**
Reviewer: **Tamara Johnson, MD, MS**

Tamara Johnson, MD, MS
NDAs 17-854, 17-862, and 21-793. ANDAs 71-402, 72-744, 73-680, and 74-703
Tardive dyskinesia class-labeling for metoclopramide products

Purpose

As part of the Food and Drug Administration Amendments Act of 2007 (FDAAA) authorization, a class labeling and Risk Evaluation and Mitigation Strategy (REMS) safety initiative for metoclopramide products was initiated. The medication guides (MG) for the above listed products are reviewed in this document. The MGs for all current metoclopramide 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 tardive dyskinesia. As the original RLD for oral solutions has been withdrawn from marketing, the four currently marketed generic oral solutions were reviewed as RLDs. This document reflects the Division of Gastroenterology Products perspective on the MGs, and was completed subsequent to reviews performed by the Office of Safety Evaluation's Division of Risk Management (DRISK) and the Division of Drug Marketing, Advertising, and Communications (DDMAC). The other REMS documents will be reviewed in an addendum document by Dr. Tamara Johnson, Division of Gastroenterology Products. The clinical review of the associated PIs was performed by Dr. Chris Leptak, Division of Gastroenterology Products. The PI review immediately precedes this document.

Materials

- 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 Labels 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 of DRISK.
- Consultation Reviews completed by Shefali Doshi and Kathleen Klemm of DDMAC.

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 the year 2000, metoclopramide utilization has increased, especially in relation to the treatment of symptomatic GERD.[3,4] Adverse event

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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.

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.

Medication Guide Review

The reviewed MGs include the language of the recent FDA-proposed boxed warning and warnings sections, regarding the risk of tardive dyskinesia, translated into a 6th-8th grade reading level, while other portions of the MGs are harmonized across the class. Changes to MGs are detailed below.

I. The boxed warning and warnings sections are translated to all the MGs as:

> **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
>
> See the section "What are the possible side effects of Metoclopramide?"

- Note: For Reglan tradename products, Reglan is substituted for Metoclopramide in the above text.

[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.

II. In the first paragraph, introductory language was added to emphasize to the patient that each specific metoclopramide product has its own particular medication guide: "If you take another product that contains metoclopramide (such as REGLAN tablets, REGLAN ODT, REGLAN injection, or metoclopramide oral syrup), you should read the Medication Guide that comes with that product. Some of the information may be different." These two statements especially make REGLAN injection patients aware of the other forms of metoclopramide.

III. Under "What are the possible side effects of Metoclopramide" – serious side effects, the description of uncontrolled spasms (dystonia) was relocated to a position after that for abnormal muscle movements (tardive dyskinesia) and before that for depression. This re-ordering is believed to better demonstrate decreasing frequency of the serious side effects.

IV. Under the serious side effects section, a statement regarding the risk population for dystonia is added to better reflect the PI. It reads as: "These spasms happen more often in children and adults under age 30." DRISK and DDMAC had similar recommendations and agreed with the final wording.

V. Under the serious side effects section, an additional statement regarding pre-existing Parkinson's disease and metoclopramide use was added to all MGs to better describe the risk: "If you already have Parkinson's disease, your symptoms may become worse while you are receiving REGLAN ODT."

VI. The common side effects profile listed in the MG is not expanded and, remains unchanged – consistent with that found in the Reglan tablets PI. This is because the adverse reaction listing in the PI does not provide estimates of frequency for each listed event. The listed CNS effects are cited in both the PI and in recent medical literature to occur in up to 10% of patients.[5,6] All other adverse reactions occur much less frequently (<2%).

VII. In the "What should I avoid while taking metoclopramide?" section, a second sentence was added to clarify the guidance on dangerous tasks. The bullet therefore reads as follows: "Do not drive, work with machines, or do dangerous tasks until you know how Metoclopramide affects you. *Metoclopramide may cause sleepiness.*"

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[5] Albibi, R and McCallum RW. Metoclopramide: Pharmacology and Clinical Application. Ann Int Med 1983;98:86-95.
[6] Lata PF and Pigarelli DLW. Chronic Metoclopramide Therapy for Diabetic Gastroparesis. Ann Pharmacotherapy 2003;37:122-126.

As each product's MG was compared to that for REGLAN tablets and harmonized by DRISK, further comments are noted if a change from the DRISK revised MGs was advocated by this reviewer or the change gained general consensus amongst the safety review team. DDMAC recommendations were mostly incorporated in the DRISK revised MGs, however, a few recommendations are visited below.

VIII. Changes specific to all metoclopramide oral solution ANDA products include:

1) The phonetic spelling of metoclopramide is now consistent across the oral solutions as "met-o-KLO-pra-mide".

IX. Changes specific to Reglan Injection (Baxter) NDA 17-862

1) The beginning of the introductory paragraph was kept as "You or your caregiver should read the Medication Guide . . . ", to address the different circumstances in which Reglan injection is administered when compared to the oral products, such as hospital, infusion center or in-home nursing care.
2) Comment: Aside from language specific to Reglan injection, the MG differed slightly from that of Reglan tablets because portions of the Reglan Injection PI needs to be updated to include missing content on 1) withdrawal symptoms and 2) the diabetic gastroparesis indication regarding symptoms relieved with metoclopramide use. Since all Reglan products were initially under one PI until sold to new sponsors, the PIs for these three products should have mostly similar language and content.

X. From the DDMAC review of the metoclopramide products, the comments that were not resolved through changes from the DRISK review were considered as follows:

1) <u>The recommendation to further elaborate on endocrine disorders, GI upset, and hypo-/hypertension.</u> Further explanation may not be as helpful for the general patient population in the MG. Endocrine disturbances do occur but mostly with long-term use -- the circumstance we are currently taking action to avoid. GI upset is nonspecific and depending on the formulation may be more nausea/vomiting or diarrhea. (Diarrhea is expected with increased GI motility.) Lastly, the change in blood pressure is specific to patients with certain conditions which are addressed elsewhere in the MG.

2) <u>The comment about the accuracy of the statement, "Rarely, men have had production of breast milk."</u> This is true as the endocrine disorders are prolactin-based changes, breast milk production is

stimulated. But these side effects would not occur with short-term use.

3) Diabetes is an independent risk factor for Tardive Dyskinesia. This was demonstrated in the psychiatry literature with antipsychotic agents that share the same mechanism of action as metoclopramide, and has been understood in gastroenterology clinical practice.[7] Ganzini et al. have also demonstrated some association of diabetes on development of tardive dyskinesia in patients.[8]

4) For the comment regarding including breast cancer on the list of conditions to tell your doctor. There is toxicological data that the use of metoclopramide or other dopamine receptor antagonists may aggravate breast cancer development. This is believed to be due to the increased prolactin levels. The information is not definitive in humans, but 1/3 of human breast cancers are prolactin-dependent. This information is written in the Toxicology and Mutagenesis section of the PI for metoclopramide products.

[7] Woerner MG, Saltx BL, Kane JM, Lieberman JA, Alvir JM. Diabetes and development of tardive dyskinesia. Am J Psychiatry 1993;150:966-968.
[8] Ganzini L et alo. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. Arch Intern med 1993;153:1469-1475.

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/s/

Christopher L Leptak
6/30/2009 07:15:13 AM
MEDICAL OFFICER

Tamara N Johnson
6/30/2009 08:51:19 AM
MEDICAL OFFICER

Nancy Snow
6/30/2009 09:02:29 AM
MEDICAL OFFICER

July 17, 2009

The attached review due to an editing error has some incorrect information on page 5 under the heading "Consults" and misrepresented DDMAC and DRISK comments. This error has been corrected in the subsequent Clinical Review signed by Christopher Leptak, MD dated 7 July, 2009 titled "Amended Tardive Dyskinesia Clinical Review of PIs."

Christopher Leptak, MD., PhD.,
NDAs 17-854, 17-862, and 21-793. ANDAs 71-402, 72-744, 73-680, and 74-703
Tardive dyskinesia class-labeling for metoclopramide-containing products

CLINICAL REVIEW

Application Type	Prior Approval Supplement Safety Labeling Changes under 505(o)(4)
Application Number(s)	NDA 17-854, 17-862, 21-793 ANDA 71-402, 72-744, 73-680, 74-703
Submit Date(s)	NDA 17-854 (051) March 25, 2009 NDA 17-862 ((061) March 26, 2009 NDA 21-793 (004) March 25, 2009 ANDA 71-402 (S-007) March 27, 2009 ANDA 72-744 (S-010) March 31, 2009 ANDA 73-680 (S-017) March 17, 2009 ANDA 74-703 (S-006) March 27, 2009
Received Date(s)	NDA 17-854 (051) March 25, 2009 NDA 17-862 ((061) March 27, 2009 NDA 21-793 (004) March 26, 2009 ANDA 71-402 (S-007) March 27, 2009 ANDA 72-744 (S-010) March 31, 2009 ANDA 73-680 (S-017) March 17, 2009 ANDA 74-703 (S-006) March 27, 2009
Amended PDUFA Goal Date (Original PDUFA date prior to two extensions to harmonize the timing of the class labeling submissions and product reviews: April 17, 2009)	NDA 17-854 (051) June 24, 2009 NDA 21-793 (004) June 24, 2009 NDA 17-862/S-061 June 25, 2009 ANDA 71-402 (S-007) June 25, 2009 ANDA 72-744 (S-010) June 29, 2009 ANDA 73-680 (S-017) June 17, 2009 ANDA 74-703 (S-006) June 25, 2009
Reviewer Name(s)	Christopher Leptak, MD/PhD Tamara Johnson, MD/MS
Review Completion Date	June 29, 2009
Therapeutic Class	Motility modifier drugs (8015655)
Indication(s)[1]	1. Relief of symptomatic gastroesophageal reflux 2. Diabetic gastroparesis
Intended Population(s)	1. Adult patients with symptomatic, documented GERD who fail to respond to conventional therapy. 2. Adult patients with acute or recurrent diabetic gastroparesis.

[1] Reglan injection (NDA 17-862) is not indicated for relief of symptomatic GERD. Additional indications for Reglan injection are prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, prevention of postoperative nausea and vomiting, small bowel intubation, radiological examination.

Christopher Leptak, MD., PhD.,
NDAs 17-854, 17-862, and 21-793. ANDAs 71-402, 72-744, 73-680, and 74-703
Tardive dyskinesia class-labeling for metoclopramide products

Product details for which this class-labeling applies

Reglan tablets (metoclopramide tablets, USP)	Alaven Pharmaceuticals, LLC	NDA 17-854
Reglan injection (metoclopramide injection, USP)	Baxter Healthcare Corporation	NDA 17-862
Reglan ODT (metoclopramide ODT, USP)	Alaven Pharmaceuticals, LLC	NDA 21-793
Metoclopramide oral solution, USP	ANI Pharmaceuticals, Inc.	ANDA 71-402
Metoclopramide oral solution, USP	Pharmaceutical Associates, Inc.	ANDA 72-744
Metoclopramide oral solution, USP	Silarx Pharmaceuticals, Inc.	ANDA 73-680
Metoclopramide oral solution, USP	Morton Grove Pharmaceuticals, Inc.	ANDA 74-703

Introduction and Reviewer's Responsibilities:

The information, review, and recommendations provided within this document apply to all the products listed above. Exceptions and discussion unique to a specific product will be indicated. Additional information will include a summary of the comments and recommendations from the consultative disciplines.

Christopher Leptak reviewed the package inserts (PIs) for all the drug products.
Tamara Johnson reviewed the medication guides (MGs) for all the drug products.
The MG review immediately follows this document.

Background

Metoclopromide-containing products are currently marketed as prescription drugs in both oral and injection formulations. The original approval for this class of products was for an injectable formulation of metoclopramide hydrochloride (NDA 17-862, Baxter Healthcare Corporation) and was approved by the FDA on February 7, 1979. A metoclopramide oral solution (NDA 18-821, Robins AH) was approved by FDA on March 25, 1983 but was subsequently discontinued. This drug product for NDA 18-821 was the referenced innovator product to which subsequent generic equivalent drug products were compared.

Although metoclopramide-containing products have historically been shown to cause a spectrum of movement disorders, especially with prolonged use, a study undertaken by FDA OSE epidemiologists (Kaplan et al., "Duration of therapy with metoclopramide: a prescription claims data study." Pharmacoepi Drug Safety, 2007, 16: 878-881) demonstrated that prolonged treatment with metoclopramide (longer than 90 days cumulative use) was common upon review of a claims data database.

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In follow up, an OSE review dated June 27, 2008, evaluated the impact of prescribing patterns in which treatment duration extended beyond that recommended in the product labelings. That review concluded that metoclopramide use in chronic conditions such as GERD should be limited to patients for whom other safer treatment options have been exhausted, and initiated only after the patient has been informed of the risks and early warning signs of metoclopramide-induced movement disorders. To heighten awareness of the risks of developing movement disorders that can become irreversible, especially in the setting of increased duration of exposure or increased cumulative dose, the review recommended the addition a risk mitigation strategy including: 1) addition of a boxed warning, 2) an appropriate risk communication plan, including a medication guide and public health advisory, 3) consideration of convening an Advisory Committee, and 4) consideration of a long-term safety study to assess the risks associated with long-term metoclopramide use.

Based on this information and recommendations, companies with marketed metoclopramide-containing products were notified in December 2008 that their products had an identified safety issue that required the submission of a Risk Evaluation and Mitigation Strategy (REMS). To guide the companies, the notification included language recommendations regarding tardive dyskinesia (TD), the most common form of irreversible movement disorder associated with long-term metoclopramide use.

On 26 February, 2009, FDA sent a letter invoking its authority under section 505(o)(4)of the FDCA to require safety related label changes to address the risk of TD associated with the use of metoclopramide-containing products based on new safety information about this risk identified since the products were approved.

Proposed Package Insert Language:

1. **Addition of Boxed Warning**

WARNING: TARDIVE DYSKINESIA

Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose.

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

Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia.

See WARNINGS

2. Addition of TD discussion to the Warnings Section of the label

WARNINGS:

Tardive Dyskinesia (see Boxed Warnings)

Treatment with metoclopramide can cause tardive dyskinesia (TD), a potentially irreversible and disfiguring disorder characterized by involuntary movements of the face, tongue, or extremities. Although the risk of TD with metoclopramide has not been extensively studied, one published study reported a TD prevalence of 20% among patients treated for at least 12 weeks. Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing TD.

Although the risk of developing TD in the general population may be increased among the elderly, women, and diabetics, it is not possible to predict which patients will develop metoclopramide-induced TD. Both the risk of developing TD and the likelihood that TD will become irreversible increase with duration of treatment and total cumulative dose.

Metoclopramide should be discontinued in patients who develop signs or symptoms of TD. There is no known effective treatment for established cases of TD, although in some patients, TD may remit, partially or completely, within several weeks to months after metoclopramide is withdrawn.

Metoclopramide itself may suppress, or partially suppress, the signs of TD, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of TD is unknown. Therefore, metoclopramide should not be used for the symptomatic control of TD.

Reviewer's Comment:

Based on review of the information FDA shared with the manufacturers of the metoclopramide-containing products, the review team made several modifications to the original proposal. These modifications were made after internal discussion between the review team and the internal consultants. After discussing the primary literature and the previous review team's recommendations, the new review team focused the TD discussion to highlight the main safety concern: extended duration of use and total cumulative dose beyond the label's recommendation. In addition, since the relevant literature studies could not readily differentiate sub-group risk factors associated with development of TD verses TD-associated with metoclopramide use, this

Christopher Leptak, MD., PhD.,
NDAs 17-854, 17-862, and 21-793. ANDAs 71-402, 72-744, 73-680, and 74-703
Tardive dyskinesia class-labeling for metoclopramide products

information was removed from the boxed warning and discussed in greater detail in the Warning Section of the label.

Consults

1. Division of Drug Marketing, Advertising, and Communications (DDMAC) and Division of Risk Management (DRISK)
The consult's review, comments, and recommendations were shared in the Memorandum dated 1 May, 2009. The comments were based on the proposed package inserts (PIs) by the companies. Of note, the comments were inclusive upon review of the entire proposed PI and thus included comments to sections that were not identified as areas of safety concern with respect to TD. Upon internal discussion, it was agreed upon that those recommendations pertinent to the identified safety issue would be addressed at this time. The main safety signal pertinent comments are summarized below with internal discussion and agreements *italicized.*

Package Insert (PI)

Boxed Warning

1. Clarification of the use of the term (b) (4) to convey the important limitation to the indication. *The term (b) (4) was removed and replaced with a "12 week" defined time frame to better delineate the duration of metoclopramide use that represents increased risk of TD development.*
2. Clarification of the age descriptive term "elderly" for the targeted patient population. *The removal of a specific age lower limit was discussed previously and the proposal of (b) (4) is best representative of the reported cases.*

Warnings

1. (b) (4)
2. (b) (4)

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NDAs 17-854, 17-862, and 21-793. ANDAs 71-402, 72-744, 73-680, and 74-703
Tardive dyskinesia class-labeling for metoclopramide products

Recommendation

This reviewer agrees that the newly proposed labeling better reflects the risk factors associated with metoclopramide-induced TD based upon a review of the literature and following discussion with Dr. Pasricha, the lead author of the most recent published summary of the topic. The recommendation is to amend the labeling as proposed.

Of note, DDMAC and DRISK consult reviews contain information beyond the TD safety issue that should be considered should the labels for metoclopramide-containing products be converted to PLR format in the future.

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NDAs 17-854, 17-862, and 21-793. ANDAs 71-402, 72-744, 73-680, and 74-703
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CLINICAL REVIEW

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Reviewer Name(s)	Christopher Leptak, MD/PhD Tamara Johnson, MD/MPH
Review Completion Date	May 22, 2009
Therapeutic Class	Motility modifier drugs (8015655)
Indication(s)[1]	1. Relief of symptomatic gastroesophageal reflux 2. Diabetic gastroparesis
Intended Population(s)	1. Adult patients with symptomatic, documented GERD who fail to respond to conventional therapy. 2. Adult patients with acute or recurrent diabetic gastroparesis.

[1] Reglan injection (NDA 17-862) is not indicated for relief of symptomatic GERD. Additional indications for Reglan injection are prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, prevention of postoperative nausea and vomiting, small bowel intubation, radiological examination.

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Metoclopramide oral solution, USP	Silarx Pharmaceuticals, Inc.	ANDA 73-680
Metoclopramide oral solution, USP	Morton Grove Pharmaceuticals, Inc.	ANDA 74-703

Introduction and Reviewer's Responsibilities:

The information, review, and recommendations provided within this document apply to all the products listed above. Exceptions and discussion unique to a specific product will be indicated. Additional information will include a summary of the comments and recommendations from the consultative disciplines.

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Tamara Johnson reviewed the medication guides (MGs) for all the drug products.

Background

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Although metoclopramide-containing products have historically been shown to cause a spectrum of movement disorders, especially with prolonged use, a study undertaken by FDA OSE epidemiologists (Kaplan et al., "Duration of therapy with metoclopramide: a prescription claims data study." Pharmacoepi Drug Safety, 2007, 16: 878-881) demonstrated that prolonged treatment with metoclopramide (longer than 90 days cumulative use) was common upon review of a claims data database.

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In follow up, an OSE review dated June 27, 2008, evaluated the impact of prescribing patterns in which treatment duration extended beyond that recommended in the product labelings. That review concluded that metoclopramide use in chronic conditions such as GERD should be limited to patients for whom other safer treatment options have been exhausted, and initiated only after the patient has been informed of the risks and early warning signs of metoclopramide-induced movement disorders. To heighten awareness of the risks of developing movement disorders that can become irreversible, especially in the setting of increased duration of exposure or increased cumulative dose, the review recommended the addition a risk mitigation strategy including: 1) addition of a boxed warning, 2) an appropriate risk communication plan, including a medication guide and public health advisory, 3) consideration of convening an Advisory Committee, and 4) consideration of a long-term safety study to assess the risks associated with long-term metoclopramide use.

Based on this information and recommendations, companies with marketed metoclopramide-containing products were notified in December 2008 that their products had an identified safety issue that required the submission of a Risk Evaluation and Mitigation Strategy (REMS). To guide the companies, the notification included language recommendations regarding tardive dyskinesia (TD), the most common form of irreversible movement disorder associated with long-term metoclopramide use.

On 26 February, 2009, FDA sent a letter invoking its authority under section 505(o)(4)of the FDCA to require safety related label changes to address the risk of TD associated with the use of metoclopramide-containing products based on new safety information about this risk identified since the products were approved.

Proposed Package Insert Language:

1. Addition of Boxed Warning

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

Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia.

See WARNINGS

2. Addition of TD discussion to the Warnings Section of the label

WARNINGS:

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Although the risk of developing TD in the general population may be increased among the elderly, women, and diabetics, it is not possible to predict which patients will develop metoclopramide-induced TD. Both the risk of developing TD and the likelihood that TD will become irreversible increase with duration of treatment and total cumulative dose.

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Metoclopramide itself may suppress, or partially suppress, the signs of TD, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of TD is unknown. Therefore, metoclopramide should not be used for the symptomatic control of TD.

Reviewer's Comment:

Based on review of the information FDA shared with the manufacturers of the metoclopramide-containing products, the review team made several modifications to the original proposal. These modifications were made after internal discussion between the review team and the internal consultants. After discussing the primary literature and the previous review team's recommendations, the new review team focused the TD discussion to highlight the main safety concern: extended duration of use and total cumulative dose beyond the label's recommendation. In addition, since the relevant literature studies could not readily differentiate sub-group risk factors associated with development of TD verses TD-associated with metoclopramide use, this

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Tardive dyskinesia class-labeling for metoclopramide products

information was removed from the boxed warning and discussed in greater detail in the Warning Section of the label.

Consults

1. Division of Drug Marketing, Advertising, and Communications (DDMAC) and Division of Risk Management (DRISK)
The consult's review, comments, and recommendations were shared in the Memorandum dated 1 May, 2009. The comments were based on the proposed package inserts (PIs) by the companies. Of note, the comments were inclusive upon review of the entire proposed PI and thus included comments to sections that were not identified as areas of safety concern with respect to TD. Upon internal discussion, it was agreed upon that those recommendations pertinent to the identified safety issue would be addressed at this time. The main safety signal pertinent comments are summarized below with internal discussion and agreements *italicized.*

Package Insert (PI)

Boxed Warning

1. Clarification of the use of the term (b) (4) to convey the important limitation to the indication. *The term* (b) (4) *was removed and replaced with a "12 week" defined time frame to better delineate the duration of metoclopramide use that represents increased risk of TD development.*

Warnings

1. Clarification that consistent language be used for all the metoclopramide-containing products with regard to TD discussion of risk factors. *The team agreed to make the appropriate changes.*

Recommendation

This reviewer agrees that the newly proposed labeling better reflects the risk factors associated with metoclopramide-induced TD based upon a review of the literature and following discussion with Dr. Pasricha, the lead author of the most recent published summary of the topic. The recommendation is to amend the labeling as proposed.

Of note, DDMAC and DRISK consult reviews contain information beyond the TD safety issue that should be considered should the labels for metoclopramide-contraining products be converted to PLR format in the future.

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/s/

Christopher L Leptak
7/7/2009 02:45:54 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-010

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:	April 24, 2009
To:	Gary Buehler, Director **Office of Generic Drugs (OGD)** Donna Griebel, M.D., Division Director **Division of Gastroenterology Products (DGP)**
Through:	Jodi Duckhorn, M.A., Team Leader **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	Metoclopramide Oral Solution, USP
Application Type/Number:	ANDA 72-744
Submission Number:	S-010
Applicant/sponsor:	Pharmaceutical Associates, Inc.
OSE RCM #:	2009-604

1 INTRODUCTION

This review is written in response to a request from the Division of Gastroenterology Drug Products (DGP) and Office of Generic Drugs (OGD) for the Division of Risk Management to review the Applicant's proposed Medication Guide for Metoclopramide Oral Solution, USP.

FDA has determined that Metoclopramide Oral Syrup, USP 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 Oral Syrup, USP. FDA has determined that Metoclopramide Oral Syrup, USP is a product with a serious a significant public health concern that meets two of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: Metoclopramide Oral Syrup, USP is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use or continue to use; Metoclopramide Oral Syrup, USP is a product for which patient labeling could help prevent serious adverse events.

2 MATERIAL REVIEWED

- Draft Metoclopramide Oral Solution, USP Prescribing Information (PI) submitted April 8, 2009.
- Metoclopramide Oral Solution, USP Medication Guide (MG) originally submitted on March 30, 2009 (paper submission), electronically submitted on April 8, 2009 and amended on April 15, 2009.

3 BACKGROUND

Pharmaceutical Associates, Inc. Abbreviated New Drug Application, ANDA 72-744, for Metoclopramide Oral Solution, USP, was approved on May 21, 1991. Metoclopramide Oral Solution is indicated for:

- **Symptomatic Gastroesophageal Reflux:**
  Reglan tablets are indicated as short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.
- **Diabetic Gastroparesis (Diabetic Gastric Stasis):**
  Reglan tablets are indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis.

OGD informed the Applicant that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for Metoclopramide Oral Solution in a Prior Approval Supplement Request letter dated February 26, 2009, due to the serious risk of Tardive Dyskinesia (TD). The only elements of the REMS will be a Medication Guide and a timetable of submission of assessments of the REMS.

The Applicant submitted a proposed REMS for Reglan (metoclopramide tablets) Tablets on March 30, 2009 (paper submission), and then electronically submitted their proposed REMS on April 8, 2009. A REMS Amendment was submitted on April 15, 2009. The REMS is

currently under review by DRISK, and will be provided to OGD and DGP under separate cover.

4 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the Applicant has a Flesch Kinkaid grade level of 11.0, and a Flesch Reading Ease score of 36.5%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised MG has a Flesch Kinkaid grade level of 8.2 and a Flesch Reading Ease score of 55.2%.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

5 CONCLUSIONS AND RECOMMENDATIONS

We have the following comments on the proposed Medication Guide:

1. The applicant's proposed MG addresses only the risk of tardive dyskinesia. The MGs for the class of Metoclopramide products are to be comprehensive in nature and the information presented in the MGs should be consistent across the products in the class. We have substantially revised the MG to make it consistent with the MGs for the other Metoclopramide products.
2. The review division should ensure consistency among all of the MGs for the Metoclopramide ANDA products for phonetic spelling, as well as referencing the product

as “Metoclopramide” and use of either lower case or upper case for spelling Metoclopramide. For brevity, we recommend using “Metoclopramide” rather than “Metoclopramide Oral Solution” throughout the MGs.

3. We have made the information in the section “What is Metoclopramide?” consistent with the labeled indication and with the other MGs for products in this class. We have added a pediatric statement at the end of this section.
4. In the section “Who should not take Metoclopramide?” we added information and revised the language in this section to make it consistent with the labeled contraindications for use of the product and with the MGs for other products in the class.
5. We have added a section called “What should I tell my doctor before taking Metoclopramide?” with information that is consistent with the product labeling and the MGs for other products in the class.
6. We have added the section “What should I avoid while taking Metoclopramide?” to convey important information about the additive effects with alcohol, and to avoid driving and operating machinery until the effects of Metoclopramide are known. This is consistent with the MGs for other products in the class.
7. We have added a section called “What are the possible side effects of Metoclopramide?” to inform patients about both the possible serious side effects and the common side effects that can occur with Metoclopramide.
    - We made this section consistent with the MGs for other products in the class.
    - We included only the common side effects listed in the REGLAN Tablets and REGLAN ODT MGs. The review division should clarify whether side effects from any other body system are relevant to include in the MG, particularly allergic reactions since no percentages are given except for CNS side effects.
    - The review division should address the questions about the common side effects across the class of products.
8. We added a section called “How should I store Metoclopramide?” for consistency with other MGs and to provide patients with information about proper storage of the product.
9. We have added the section “General information about Metoclopramide?”
    - We added the following verbatim statement in accordance with 21 CFR 208.20 (b)(8)(i):

        Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

    - We revised the following verbatim statement so that it is in accordance with 21CFR 208.2 (a) (6):

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

    - Add the name and address of the manufacturer, packer, or distributor following this section.

Please let us know if you have any questions.

Following this page, 12 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/

Sharon Mills
4/24/2009 02:42:32 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
4/24/2009 03:16:34 PM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 72-744/S-010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

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MAR 31 2009
OGD

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Greenville, SC 29605
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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

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

4/3/2009 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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- ☐ PRE-NDA MEETING
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- ☐ RESUBMISSION
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- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
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- ☐ CLINICAL
- ☐ NONCLINICAL

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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 73-680 Silarx (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
4/6/2009 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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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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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

ANDA 72-744/S-010 **PRIOR APPROVAL SUPPLEMENT**

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

Dear Madam:

We have received your supplemental new drug application submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

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

ANDA Number: 72-744/S-010

Date of supplement: March 30, 2009

Date of receipt: March 31, 2009

On February 26, 2009, we sent a letter invoking our authority 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 identified since the product was approved. You were directed to submit a prior-approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On March 31, 2009, FDA received your prior-approval supplement that contained your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplement and, if we disagree with the proposed changes, to initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that a 30-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for the supplement, ANDA 72-744/S-010, ends on May 30, 2009.

If you have 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

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/s/

Robert L. West
5/4/2009 02:12:07 PM
Deputy Director, for Gary Buehler

From: Park, Sarah Soojung
Sent: Wednesday, May 06, 2009 3:33 PM
To: 'kmcdonald@paipharma.com'
Cc: Lemley, Carrie; Lee, Koung U
Subject: 72-744/S-010 Metoclopramide Oral Solution USP, 5 mg/5 mL

Attachments: Metoclopramide Boxed Warnings Final Labeling 04 15 09.doc; ANDA 72-744 Pharm Assoc Metoclopramide MG final 2.doc

Good afternoon,

This email is in reference to your ANDA 72-744/S-010 for Metoclopramide Oral Solution USP, 5 mg/5 mL.

Please see the enclosed proposed changes to the Metoclopramide Oral Solution USP, 5 mg/5 mL package insert and Medication Guide. Please review the changes proposed by the Agency and incorporate accordingly.

If possible, please respond to the proposed changes as an amendment to the supplement by **Tuesday, May 12, 2009**. Please include a Word copy with your proposed Track Changes (if any).


Metoclopramide Boxed Warnings | ANDA 72-744 Pharm Assoc Metoc

Thank you,

Sarah Park

Sarah Park, Pharm.D.
Labeling Reviewer
Division of Labeling and Program Support
Office of Generic Drugs
Food and Drug Administration
240-276-8995
240-276-8999 (fax)
sarah.park@fda.hhs.gov

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/s/

Soojung Sarah Park
5/6/2009 03:47:53 PM
LABELING REVIEWER

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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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

ANDA 72-744/S-010

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 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Metoclopramide Oral Solution USP, 5 mg/5 mL.

On February 26, 2009, we sent a letter invoking our authority 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 identified since the product was approved. You were directed to submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On March 31, 2009, FDA received your prior approval supplement that contained your proposed safety related labeling changes, including a Medication Guide. Section 505(o) requires FDA to promptly review the supplement and if we disagree with the proposed changes, to initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

We refer to the letter we sent to you on May 4, 2009, informing you that we determined that a 30-day extension of the discussion period was warranted to allow us to complete our review and reach agreement on the content of the labeling.

This letter is to inform you that we have determined that an additional 30-day extension of the discussion period is warranted. Therefore, the discussion period for this supplement, ANDA 72-744/S-010, ends on June 29, 2009.

If you have any questions, please contact 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

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/s/

Gary Buehler

5/18/2009 02:28:22 PM

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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