CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

17-854/S051

21-793/S004

Trade Name:	Reglan Tablets Reglan Orally Disinegrating Tablets
Generic Name:	(metoclopramide)
Sponsor:	Alaven Pharmaceutical LLC
Approval Date:	June 30, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL LETTER

17-854/S051
21-793/S004

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-854/S-051
NDA 21-793/S-004

Alaven Pharmaceuticals, LLC
Attention: Mary Alonso
Director, Quality Assurance and Regulatory Affairs
200 North Cobb Parkway, Suite 428
Marietta, GA 30062

Dear Ms. Alonso:

Please refer to your supplemental NDA 17-854/S-051 for Reglan (metoclopramide) Tablets and supplemental NDA 21-793/S-004 for Reglan ODT (metoclopramide) Orally Disintegrating Tablets submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA).

We acknowledge receipt of your submissions dated March 3, March 25, May 12, May 15, June 23, June 25, June 26, 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 Reglan (metoclopramide) Tablets and Reglan ODT (metoclopramide) Orally Disintegrating Tablets. This information pertains to the risk of tardive dyskinesia.

These supplemental new drug applications provide for revisions to the labeling for Reglan (metoclopramide) Tablets and Reglan ODT (metoclopramide) Orally Disintegrating Tablets consistent with our February 26, 2009, letter and correspondences between FDA and Alaven dated March 30, May 6, May 18, June 18, June 24, June 26, 2009.

We have completed our review of this supplemental application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Your approved Medication Guide will become part of the Risk Evaluation and Mitigation Strategy (REMS) in pending supplements NDA 17-854/S-052 and NDA 21-793/S-005.

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 NDA 17-854/S-052 and NDA 21-793/S-005."** In addition, within 21 days of the date of this letter, amend any pending supplement for these NDAs.

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 text and in the required format may render the product misbranded and an unapproved new 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 NDA 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 NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

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

Enclosure: 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/

Joyce Korvick
6/30/2009 05:04:13 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-854/S051
21-793/S004

LABELING

reglan® tablets (metoclopramide tablets, 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

For oral administration, reglan® tablets (metoclopramide tablets, USP) 10 mg are white, scored, capsule-shaped tablets engraved REGLAN on one side and SP 10 on the opposite side.

Each tablet contains:
Metoclopramide base ..... 10 mg
(as the monohydrochloride monohydrate)

Inactive Ingredients
Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Stearic Acid.

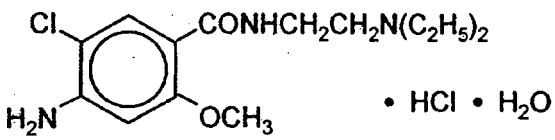
reglan® tablets (metoclopramide tablets, USP) 5 mg are green, elliptical-shaped tablets engraved REGLAN 5 on one side and SP on the opposite side.

Each tablet contains:
Metoclopramide base ..... 5 mg
(as the monohydrochloride monohydrate)

Inactive Ingredients

Corn starch, D&C Yellow 10 Aluminum Lake, FD&C Blue 1 Aluminum Lake, Lactose, Microcrystalline Cellulose, Silicon Dioxide, Stearic Acid.

Metoclopramide hydrochloride is a white crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5- chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its molecular formula is $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$. Its molecular weight is 354.3.



CLINICAL PHARMACOLOGY

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the 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 the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5 mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the 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 the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare (see **WARNINGS**). Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with 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 crossover study of 18 subjects. Peak plasma concentrations occur at about 1 to 2 hr 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, the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5 to 6 hr. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hr. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

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

Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life. The kinetics of metoclopramide in the 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 Protein Binding	~ 30%
$t_{1/2}$ (hr)	5 to 6
Oral Bioavailability	80%±15.5%

In pediatric patients, the 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 whether the pharmacokinetics of metoclopramide in adults and the pediatric population are similar. Although there are insufficient data to support the efficacy of metoclopramide in pediatric patients with symptomatic gastroesophageal reflux (GER) or cancer chemotherapy-related nausea and vomiting, its pharmacokinetics have been studied in these 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 tenth dose was 2-fold (56.8 µg/L) higher compared to that observed after the first dose (29 µg/L) indicating drug accumulation with repeated dosing. After the tenth 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 those observed after the first dose. In the youngest patient (age, 3.5 weeks), metoclopramide half-life after the first and the tenth dose (23.1 and 10.3 hr, respectively) was significantly longer compared to other infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at birth.

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 chemotherapy (mean age, 11.7 years; range, 7 to 14 yr) for prophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time zero ranged from 65 to 395 µg/L (mean, 152 µg/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 3.0 L/kg (range, 1.0 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 control emesis. After the last dose, the peak serum concentrations of metoclopramide ranged from

1060 to 5680 µg/L. The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5 hr (range, 2.0 to 12.5 hr), 0.37 L/h/kg (range, 0.10 to 1.24 L/h/kg), and 1.93 L/kg (range, 0.95 to 5.50 L/kg), respectively.

INDICATIONS AND USAGE

The use of reglan® tablets is recommended for adults only. Therapy should not exceed 12 weeks in duration.

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.

The principal effect of metoclopramide is on symptoms of postprandial and daytime heartburn with less observed effect on nocturnal symptoms. If symptoms are confined to particular situations, such as following the evening meal, use of metoclopramide as single doses prior to the provocative situation should be considered, rather than using the drug throughout the day. Healing of esophageal ulcers and erosions has been endoscopically demonstrated at the 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 with documented lesions should be monitored endoscopically.

Diabetic Gastroparesis (Diabetic Gastric Stasis)
reglan® tablets (metoclopramide tablets, USP) is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) appear to respond to reglan® within different time intervals. Significant relief of nausea occurs early and continues to improve over a three-week period. Relief of vomiting and anorexia may precede the relief of abdominal fullness by one week or more.

CONTRAINDICATIONS

Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

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 without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the 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 than 30 years of age and are even more frequent at higher doses. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion 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 these symptoms should occur, inject 50 mg diphenhydramine hydrochloride intramuscularly, and they usually will subside. Benztropine mesylate, 1 to 2 mg intramuscularly, may also be used to reverse these reactions.

Parkinsonian-like symptoms have occurred, more commonly within the first 6 months after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside within 2 to 3 months following discontinuance of metoclopramide. Patients with preexisting 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 (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.

Neuroleptic Malignant Syndrome (NMS)
There have been rare reports of an uncommon but potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) associated with metoclopramide. Clinical manifestations of NMS include hyperthermia, muscle rigidity, altered consciousness, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac arrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, malignant hyperthermia, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of metoclopramide and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. Bromocriptine and dantrolene 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 with hypertension.

Because metoclopramide produces a transient increase in plasma aldosterone, certain patients, especially those with cirrhosis or congestive heart failure, may be at risk of developing fluid retention and volume overload. If these side effects occur at any time during metoclopramide therapy, the drug should be discontinued.

Adverse reactions, especially those involving the nervous system, may occur after stopping the use of reglan®. A small number of patients may experience a withdrawal period after stopping reglan® that could include dizziness, nervousness, and/or headaches.

Information for Patients

The use of reglan® is recommended for adults only. Metoclopramide may impair the 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.

For additional information, patients should be instructed to see the Medication Guide for reglan® tablets.

Drug Interactions

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

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

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

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of food to the intestines and thus 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 prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

An Ames mutagenicity test performed on metoclopramide was negative.

Pregnancy Category B
Reproduction studies performed in rats, mice and rabbits by the I.V., I.M., S.C., and oral routes at maximum levels ranging from 12 to 250 times the human dose have demonstrated no impairment of fertility or significant harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction 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 mother.

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

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

The safety profile of metoclopramide in adults cannot be extrapolated to pediatric patients. Dystonias and other extrapyramidal reactions associated with metoclopramide

are more common in the pediatric population than in adults. (See **WARNINGS** and **ADVERSE REACTIONS - Extrapyramidal Reactions.**)

Geriatric Use
Clinical studies of reglan® did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects.

The risk of developing parkinsonian-like side effects increases with ascending dose. Geriatric patients should receive the lowest dose of reglan® that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving reglan®, reglan® should generally be discontinued before initiating any specific anti-parkinsonian 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 reglan® users. Sedation may cause confusion and manifest as over-sedation in the elderly (see **CLINICAL PHARMACOLOGY, PRECAUTIONS – Information for Patients** and **ADVERSE REACTIONS – CNS Effects**).

reglan® is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION – USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT**).

For these reasons, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, 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 with NADH-cytochrome b_5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended (see **OVERDOSAGE**).

ADVERSE REACTIONS

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

CNS Effects
Restlessness, drowsiness, fatigue, and lassitude occur in approximately 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 drowsiness 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 with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (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, foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

Neuroleptic Malignant Syndrome
Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported. This potentially fatal syndrome is comprised of the symptom complex of hyperthermia, altered consciousness, muscular rigidity, and autonomic dysfunction (see **WARNINGS**).

Endocrine Disturbances
Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia (see **PRECAUTIONS**). Fluid retention secondary to transient elevation of aldosterone (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 diarrhea.

Hepatic
Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

Renal
Urinary frequency and incontinence.

Hematologic
A few cases of neutropenia, leukopenia, or agranulocytosis, generally without clearcut

relationship to metoclopramide. Methemoglobinemia, in adults and especially with overdosage in neonates (see **OVERDOSAGE**). Sulfhemoglobinemia in adults.

Allergic Reactions
A few cases of rash, urticaria, or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.

Miscellaneous
Visual disturbances. Porphyria.

OVERDOSAGE

Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions. Anticholinergic or antiparkinson drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours.

Hemodialysis removes relatively little metoclopramide, probably because of the small amount of the 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 through dialysis. Dialysis is not likely to be an effective method of drug removal in overdose situations.

Unintentional overdose due to misadministration has been reported in infants and children with the use of metoclopramide oral solution. While there was no consistent pattern to the reports associated with these overdoses, events included seizures, extrapyramidal reactions, and lethargy.

Methemoglobinemia 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 the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal (see **PRECAUTIONS – Other Special Populations**).

DOSAGE AND ADMINISTRATION

Therapy with reglan® tablets should not exceed 12 weeks in duration.

For the Relief of Symptomatic Gastroesophageal Reflux
Administer from 10 mg to 15 mg reglan® (metoclopramide hydrochloride, 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 the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

Experience with esophageal erosions and ulcerations is limited, but healing has thus far been documented in one controlled trial using q.i.d. therapy at 15 mg/dose, and this 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 than 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 the likelihood of continued well-being upon drug discontinuation.

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

Administration of 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, reglan® therapy should be reinstituted at the earliest manifestation.

USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT
Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

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

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

HOW SUPPLIED

Each white, capsule-shaped, scored reglan® tablet (metoclopramide tablets, USP) contains 10 mg metoclopramide base (as the monohydrochloride monohydrate). Available in:

Bottles of 100 tablets (NDC 0091-6701-63)

Each green, elliptical-shaped reglan® tablet (metoclopramide tablets, USP) contains 5 mg metoclopramide base (as the monohydrochloride monohydrate). Available in:

Bottles of 100 tablets (NDC 0091-6705-63)

Dispense tablets in tight, light-resistant container.

Tablets should be stored at controlled room temperature, between 20°C and 25°C (68°F and 77°F).

SCHWARZ
PHARMA
Milwaukee, WI 53201, USA

Rev. 06/09

Medication Guide

REGLAN (REG-lan) Tablets
(metoclopramide tablets)

Read the Medication Guide that comes with REGLAN 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 injection, REGLAN ODT, or metoclopramide oral syrup), 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 REGLAN?

REGLAN 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 REGLAN. There is no treatment for TD, but symptoms may lessen or go away over time after you stop taking REGLAN.

Your chances for getting TD go up:

- the longer you take REGLAN and the more REGLAN you take. You should not take REGLAN 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 REGLAN.

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 REGLAN?" for more information about side effects.

What is REGLAN?

REGLAN 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. REGLAN 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. REGLAN helps treat symptoms such as nausea, vomiting, heartburn, feeling full long after a meal, and loss of appetite. Not all these symptoms get better at the same time.

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

Who should not take REGLAN?

Do not take REGLAN if you:
- have stomach or intestine problems that could get worse with REGLAN, such as bleeding, blockage or a tear in the stomach or bowel wall
- have an adrenal gland tumor called a pheochromocytoma
- are allergic to REGLAN or anything in it. See the end of this Medication Guide for a list of ingredients in REGLAN.
- take medicines that can cause uncontrolled movements, such as medicines for mental illness
- have seizures

What should I tell my doctor before taking REGLAN?

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. REGLAN 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 REGLAN will harm your unborn baby.
- you are breast-feeding. REGLAN 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 REGLAN.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. REGLAN 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 REGLAN until you talk with your doctor.

Especially tell your doctor if you take:
- another medicine that contains metoclopramide, such as REGLAN ODT, or metoclopramide oral syrup
- a blood pressure medicine
- a medicine for depression, especially an Monoamine Oxidase Inhibitor (MAOI)
- insulin
- a medicine that can make you sleepy, such an anti-anxiety medicine, sleep medicines, and narcotics.

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

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

How should I take REGLAN?

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

What should I avoid while taking REGLAN?

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

What are the possible side effects of REGLAN?

Reglan can cause serious side effects, including:

- **Abnormal muscle movements.** See "What is the most important information I need to about know REGLAN?"
- **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 REGLAN become depressed. You may have thoughts about hurting or killing yourself. Some people who take Reglan have ended their own lives (suicide).
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a very rare but very serious condition that can happen with Reglan. 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 REGLAN.

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

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

Common side effects of Reglan include:

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

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

You may still have side effects after stopping REGLAN. You may have symptoms from stopping (withdrawal) REGLAN 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 REGLAN.

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 REGLAN?

- Keep REGLAN at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep REGLAN in the bottle it comes in. Keep the bottle closed tightly.

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

General information about REGLAN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REGLAN for a condition for which it was not prescribed. Do not give REGLAN 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 REGLAN. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about REGLAN that is written for health professionals. For more information, go to www.alavenpharma.com or call 1-888-317-0001.

What are the ingredients in REGLAN?

Active ingredient: metoclopramide
Inactive ingredients:

REGLAN 10 mg tablets: magnesium stearate, mannitol, microcrystalline cellulose, stearic acid

REGLAN 5 mg tablets: corn starch, D&C yellow 10 aluminum lake, FD&C blue 1 aluminum lake, lactose, microcrystalline cellulose, silicon dioxide, stearic acid

Manufactured for

Alaven Pharmaceutical LLC, Marietta, GA 30062

Revised June 2009

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

REGLAN ODT™
(metoclopramide orally disintegrating tablets)

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.

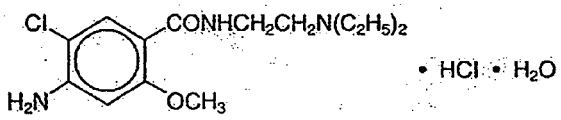
Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia.

See WARNINGS

DESCRIPTION

REGLAN ODT™ (metoclopramide orally disintegrating tablets) is an orally administered formulation of metoclopramide which disintegrates on the tongue.

Metoclopramide hydrochloride is a white crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its molecular formula is $C_{14}H_{22}ClN_3O_2 \bullet HCl \bullet H_2O$. Its molecular weight is 354.3.



Each orally disintegrating tablet contains either 5 mg or 10 mg of metoclopramide base (as the monohydrochloride monohydrate) and the following inactive ingredients: aspartame, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, aminoalkyl methacrylate copolymer, microcrystalline cellulose, natural and artificial orange flavor and povidone.

CLINICAL PHARMACOLOGY

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the 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 the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5 mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the 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 the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare (see **WARNINGS**). Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with 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 crossover study of 18 subjects. Peak plasma concentrations occur at about 1 to 2 hr 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, the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The mean elimination half-life of metoclopramide is approximately 7 hr

after administration of REGLAN ODT™. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.
Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hr. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

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

Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life. The kinetics of metoclopramide in the 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 Protein Binding	~ 30%
$t_{½}$ (hr)	~ 7
Oral Bioavailability	80% ± 15.5%

In pediatric patients, the 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 whether the pharmacokinetics of metoclopramide in adults and the pediatric population are similar. Although there are insufficient data to support the efficacy of metoclopramide in pediatric patients with symptomatic gastroesophageal reflux (GER) or cancer chemotherapy-related nausea and vomiting, its pharmacokinetics have been studied in these 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 tenth dose was 2-fold (56.8 µg/L) higher compared to that observed after the first dose (29 µg/L) indicating drug accumulation with repeated dosing. After the tenth 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 those observed after the first dose. In the youngest patient (age, 3.5 weeks),

metoclopramide half-life after the first and the tenth dose (23.1 and 10.3 hr, respectively) was significantly longer compared to other infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at birth.

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 chemotherapy (mean age, 11.7 years; range, 7 to 14 yr) for prophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time zero ranged from 65 to 395 μg/L (mean, 152 μg/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 3.0 L/kg (range, 1.0 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 control emesis. After the last dose, the peak serum concentrations of metoclopramide ranged from 1060 to 5680 μg/L. The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5 hr (range, 2.0 to 12.5 hr), 0.37 L/h/kg (range, 0.10 to 1.24 L/h/kg), and 1.93 L/kg (range, 0.95 to 5.50 L/kg), respectively.

INDICATIONS AND USAGE

The use of REGLAN ODT™ is recommended for adults only. Therapy should not exceed 12 weeks in duration.

Symptomatic Gastroesophageal Reflux

REGLAN ODT™ is indicated as short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.

The principal effect of metoclopramide is on symptoms of postprandial and daytime heartburn with less observed effect on nocturnal symptoms. If symptoms are confined to particular situations, such as following the evening meal, use of metoclopramide as single doses prior to the provocative situation should be considered, rather than using the drug throughout the day. Healing of esophageal ulcers and erosions has been endoscopically demonstrated at the end of a 12-week trial using doses of 15 mg four times daily. As there is no documented correlation between symptoms and healing of esophageal lesions, patients with documented lesions should be monitored endoscopically.

Diabetic Gastroparesis (Diabetic Gastric Stasis)

REGLAN ODT™ is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) appear to respond to metoclopramide within different time intervals. Significant relief of nausea occurs early and continues to improve over a three-week period. Relief of vomiting and anorexia may precede the relief of abdominal fullness by one week or more.

CONTRAINDICATIONS

Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

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 without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the 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 than 30 years of age and are even more frequent at higher doses. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion 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 these symptoms should occur, inject 50 mg diphenhydramine hydrochloride intramuscularly, and they usually will subside. Benztropine mesylate, 1 to 2 mg intramuscularly, may also be used to reverse these reactions.

Parkinsonian-like symptoms have occurred, more commonly within the first 6 months after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside within 2 to 3 months following discontinuance of metoclopramide. Patients with preexisting 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 (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.

Neuroleptic Malignant Syndrome (NMS)

There have been rare reports of an uncommon but potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) associated with metoclopramide. Clinical manifestations of NMS include hyperthermia, muscle rigidity, altered consciousness, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac arrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, malignant hyperthermia, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of metoclopramide and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. Bromocriptine and dantrolene 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 with hypertension.

Because metoclopramide produces a transient increase in plasma aldosterone, certain patients, especially those with cirrhosis or congestive heart failure, may be at risk of developing fluid retention and volume overload. If these side effects occur at any time during metoclopramide therapy, the drug should be discontinued.

Adverse reactions, especially those involving the nervous system, may occur after stopping the use of REGLAN ODT™. A small number of patients may experience a withdrawal period after stopping REGLAN ODT™ that could include dizziness, nervousness, and/or headaches.

Information for Patients
Patients should be instructed not to remove REGLAN ODT™ orally disintegrating tablets from the bottle until just prior to dosing. With dry hands, the tablet should be removed from the bottle and immediately placed on the tongue to disintegrate and be swallowed with the saliva. The tablet typically disintegrates in about one and one-half minutes. Administration with liquid is not necessary.

The use of REGLAN ODT™ orally disintegrating tablets is recommended for adults only. Metoclopramide may impair the 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.

For additional information, patients should be instructed to see the Medication Guide for REGLAN ODT™.

Phenylketonurics
Phenylketonuric patients should be informed that REGLAN ODT™ contains phenylalanine 4.2 mg per 5 mg orally disintegrating tablet and 8.3 mg per 10 mg orally disintegrating tablet.

Drug Interactions
The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

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

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

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of food to the

intestines and thus 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 of metoclopramide up to 40 mg/kg/day (about 5 times the maximum recommended human dose on surface area basis). Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

In a rat model for assessing the tumor promotion potential, a two-week oral treatment with metoclopramide at a dose of 260 mg/kg/day (about 35 times the maximum recommended human dose on surface area basis) enhanced the tumorigenic effect of N-nitrosodiethylamine.

Metoclopramide was positive in the *in vitro* Chinese hamster lung cell/HGPRT forward mutation assay for mutagenic effects and the *in vitro* human lymphocyte chromosome aberration assay for clastogenic effects. It was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat and human hepatocytes and the *in vivo* rat micronucleus assay.

Metoclopramide at intramuscular doses up to 20 mg/kg/day in male and female rats (about 3 times the maximum recommended human dose on surface area basis) was found to have no effect on fertility and reproductive performance.

Pregnancy Teratogenic Effects: Pregnancy Category B
Teratology studies have been performed in rats at oral doses up to 45 mg/kg/day (about 6 times the maximum recommended human dose on surface area basis), and in rabbits at oral doses up to 45 mg/kg/day (about 12 times the maximum recommended human dose on surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction 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 mother. Because of the potential for serious adverse reactions in nursing infants from metoclopramide and because of the potential for tumorigenicity and tumor promoting potential shown for metoclopramide in rats, a decision should be made whether to

discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established (see **OVERDOSAGE**). Care should be exercised in administering metoclopramide to neonates since prolonged clearance may produce excessive serum concentrations (see **CLINICAL PHARMACOLOGY—Pharmacokinetics**). In addition, neonates have reduced levels of NADH-cytochrome b_5 reductase which, in combination with the aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia (see **OVERDOSAGE**).

The safety profile of metoclopramide in adults cannot be extrapolated to pediatric patients. Dystonias and other extrapyramidal reactions associated with 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 whether elderly subjects respond differently from younger subjects.

The risk of developing parkinsonian-like side effects increases with ascending dose. Geriatric patients should receive the lowest dose of REGLAN ODT™ that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving REGLAN ODT™, REGLAN ODT™ should generally be discontinued before initiating any specific anti-parkinsonian 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 the elderly (see **CLINICAL PHARMACOLOGY, PRECAUTIONS – Information for Patients** and **ADVERSE REACTIONS – CNS Effects).**

Metoclopramide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION – Use in Patients with Renal or Hepatic Impairment**).

For these reasons, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, 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 with NADH-cytochrome b_5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In

patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended (see **OVERDOSAGE**).

ADVERSE REACTIONS

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

CNS Effects

Restlessness, drowsiness, fatigue, and lassitude occur in approximately 10% of patients receiving the most commonly prescribed dosage of 10 mg four times daily. (see **PRECAUTIONS**). Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation (see **WARNINGS**) occur less frequently. The incidence of drowsiness is greater at higher doses. There are isolated reports of convulsive seizures without clear-cut relationship to metoclopramide. Rarely, hallucinations have been reported.

Extrapyramidal Reactions (EPS)

Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (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, foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

Neuroleptic Malignant Syndrome

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported. This potentially fatal syndrome is comprised of the symptom complex of hyperthermia, altered consciousness, muscular rigidity, and autonomic dysfunction (see **WARNINGS**).

Endocrine Disturbances

Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia (see **PRECAUTIONS**). Fluid retention secondary to transient elevation of aldosterone (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 diarrhea.

Hepatic
Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

Renal
Urinary frequency and incontinence.

Hematologic
A few cases of neutropenia, leukopenia, or agranulocytosis, generally without clear-cut relationship to metoclopramide. Methemoglobinemia, in adults and especially with overdosage in neonates (see **OVERDOSAGE**). Sulfhemoglobinemia in adults.

Allergic Reactions
A few cases of rash, urticaria, or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.

Miscellaneous
Visual disturbances. Porphyria.

The adverse experience profile seen with REGLAN ODT™ orally disintegrating tablets in 21 healthy subjects, was similar to that seen with Reglan® Tablets.

OVERDOSAGE

Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions. Anticholinergic or antiparkinson drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours.

Hemodialysis removes relatively little metoclopramide, probably because of the small amount of the 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 through dialysis. Dialysis is not likely to be an effective method of drug removal in overdose situations.

Unintentional overdose due to misadministration has been reported in infants and children with the use of metoclopramide oral solution. While there was no consistent pattern to the reports associated with these overdoses, events included seizures, extrapyramidal reactions, and lethargy.

Methemoglobinemia 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 the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal (see **PRECAUTIONS – Other Special Populations**).

DOSAGE AND ADMINISTRATION

Therapy with REGLAN ODT™ should not exceed 12 weeks in duration.

Instructions for Use/Handling REGLAN ODT™
Just prior to administration, remove the REGLAN ODT™ orally disintegrating tablet from the bottle with dry hands. The tablet should be removed from the bottle and immediately placed on the tongue, to disintegrate and be swallowed with the saliva. The tablet typically disintegrates in about one and one-half minutes. Administration with liquid is not necessary.

For the Relief of Symptomatic Gastroesophageal Reflux
Administer from 10 mg to 15 mg of REGLAN ODT™ orally up to four times daily, 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 the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

Experience with esophageal erosions and ulcerations is limited, but healing has thus far been documented in one controlled trial using four times daily therapy at 15 mg/dose, and this 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 than 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 REGLAN ODT™ 30 minutes before each meal and at bedtime for two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation.

The initial route of administration should be determined by the severity of the presenting symptoms. If only the earliest manifestations of diabetic gastric stasis are present, oral administration of REGLAN ODT™ may be initiated. However, if severe symptoms are present, therapy should begin with metoclopramide injection (consult labeling of the injection prior to initiating parenteral administration).

Administration of 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, REGLAN ODT™ therapy should be reinstituted at the earliest manifestation.

Use in Patients with Renal or Hepatic Impairment
Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

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

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

HOW SUPPLIED
REGLAN ODT™ (metoclopramide orally disintegrating tablets) 5 mg base (as the monohydrochloride monohydrate) are white, round, flat-faced, orange-flavored and engraved "SP331" on one side and "5" on the other side. They are supplied as follows:

Bottles of 100	NDC 0091-3331-01

REGLAN ODT™ (metoclopramide orally disintegrating tablets) 10 mg base (as the monohydrochloride monohydrate) are white, round, flat-faced, orange-flavored and engraved "SP332"on the one side and "10" on the other side. They are supplied as follows:

Bottles of 100	NDC 0091-3332-01

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.

Dispense in a tight, light-resistant container as defined in the USP/NF.

Manufactured for:

SCHWARZ
PHARMA

Milwaukee, WI 53201, USA

By: CIMA LABS INC.®
Eden Prairie, MN 55344, USA

REGLAN ODT™ uses CIMA LABS INC® U.S. Patent Nos. 6,024,981 and 6,221,392.

Reglan® is a registered trademark of SRZ Properties, Inc.

Rev. 06/09

Medication Guide

REGLAN ODT (REG-lan Oh-dee-tee)
(metoclopramide orally disintegrating tablets)

Read the Medication Guide that comes with REGLAN ODT 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 injection, or metoclopramide oral syrup), 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 REGLAN ODT?

REGLAN ODT 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 REGLAN ODT. There is no treatment for TD, but symptoms may lessen or go away over time after you stop taking REGLAN ODT.

Your chances for getting TD go up:

- the longer you take REGLAN ODT and the more REGLAN ODT you take. You should not take REGLAN ODT 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 REGLAN ODT.

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 REGLAN ODT?" for more information about side effects.

What is REGLAN ODT?

REGLAN ODT 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. REGLAN ODT 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. REGLAN ODT helps treat symptoms such as nausea, vomiting, heartburn, feeling full long after a meal, and loss of appetite. Not all these symptoms get better at the same time.

It is not known if REGLAN ODT is safe and works in children.

Who should not take REGLAN ODT?

Do not take REGLAN ODT if you:

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

What should I tell my doctor before taking REGLAN ODT?

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. REGLAN ODT may cause your body to hold fluids.
- diabetes. Your dose of insulin may need to be changed.
- breast cancer
- phenylketonuria. REGLAN ODT contains aspartame.
- you are pregnant or plan to become pregnant. It is not known if REGLAN ODT will harm your unborn baby.
- you are breast-feeding. REGLAN ODT 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 REGLAN ODT.

Tell your doctor about all the medicines you take including, prescription and non-prescription medicines, vitamins, and herbal supplements. REGLAN ODT 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 REGLAN ODT until you talk with your doctor.

Especially tell your doctor if you take:

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

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

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

How should I take REGLAN ODT?

- REGLAN ODT comes as a tablet that melts in your mouth.
- Take REGLAN ODT exactly as your doctor tells you. Do not change your dose unless your doctor tells you.
- You should not take REGLAN ODT for more than 12 weeks.
- To take REGLAN ODT:
  - Leave the tablet in the bottle until you are ready to take it.
  - Use dry hands to take out a tablet. If your hands are wet, the tablets will melt.
  - Put the tablet on your tongue right away. Let it melt and then swallow. You do not need water to take REGLAN ODT.
- If you take too much REGLAN ODT, call your doctor or Poison Control Center right away.

What should I avoid while taking REGLAN ODT?

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

What are the possible side effects of REGLAN ODT?

Reglan ODT can cause serious side effects, including:

- **Abnormal muscle movements.** See "What is the most important information I should know about REGLAN ODT?"
- **Uncontrolled spasm 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 REGLAN ODT become depressed. You may have thoughts about hurting or killing yourself. Some people who take REGLAN ODT have ended their own lives (suicide).
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a rare but very serious condition that can happen with REGLAN ODT. 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 REGLAN ODT.

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 can not stop or control
- have muscle movements that are new or unusual

Common side effects include:
- feeling restless, sleepy, tired, dizzy, or exhausted
- headache
- confusion
- trouble sleeping

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

You may still have side effects after you stop REGLAN ODT. You may have symptoms from stopping (withdrawal) REGLAN ODT 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 REGLAN ODT.

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

How do I store REGLAN ODT?
- Keep REGLAN ODT at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep REGLAN ODT in the bottle it comes in. Keep the bottle closed tightly.
- Keep REGLAN ODT dry so it does not melt.

Keep REGLAN ODT and all medicines out of the reach of children.

General information about REGLAN ODT

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REGLAN ODT for a condition for which it was not prescribed. Do not give REGLAN ODT 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 REGLAN ODT. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about REGLAN ODT that is written for health professionals. For more information go to www.alavenpharma.com or call 1-888-317-0001.

What are the ingredients in REGLAN ODT?

Active ingredient: metoclopramide

Inactive ingredients: aspartame, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, aminoalkyl methacrylate copolymer, microcrystalline cellulose, natural and artificial orange flavor, povidone

Manufactured for

Alaven Pharmaceutical LLC, Marietta, GA 30062

Revised June 2009
This Medication Guide has been approved by the U.S. Food and Drug Administration.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-854/S051

21-793/S004

MEDICAL REVIEW(S)

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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Tardive dyskinesia class-labeling for metoclopramide products

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.,
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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.*
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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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.

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/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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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.

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.

Christopher Leptak, MD., PhD.,
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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

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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
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MEDICAL OFFICER

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/

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6/30/2009 07:15:13 AM
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Tamara N Johnson
6/30/2009 08:51:19 AM
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6/30/2009 09:02:29 AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-854/S051

21-793/S004

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 20, 2009
To:	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):	Reglan (metoclopramide tablets, USP) Tablets
Application Type/Number:	NDA 17-854
Submission Number:	S-051
Applicant/sponsor:	Alaven Pharmaceutical, LLC
OSE RCM #:	2009-604

1 INTRODUCTION

This review is written in response to a request from the Division of Gastroenterology Products (DGP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG).

FDA has determined that Reglan (metoclopramide tablets, USP) Tablets 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 Reglan (metoclopramide tablets, USP) Tablets. FDA has determined that Reglan (metoclopramide tablets, USP) Tablets are 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: Reglan (metoclopramide tablets, USP) Tablets 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; Reglan (metoclopramide tablets, USP) Tablets is a product for which patient labeling could help prevent serious adverse events.

2 MATERIAL REVIEWED

- Draft Reglan (metoclopramide tablets, USP) Tablets Prescribing Information (PI) submitted on March 25, 2009.
- Draft Reglan (metoclopramide tablets, USP) Tablets Medication Guide (MG) submitted on March 25, 2009.

3 BACKGROUND

Reglan (metoclopramide tablets, USP) Tablets, NDA 17-854, were approved December 30, 1980. Reglan (metoclopramide tablets, USP) Tablets are 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.

DGP informed the Applicant that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for Reglan tablets (metoclopramide tablets 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 was notified in the same letter that a REMS is also required for NDA 21-793, Reglan ODT (metoclopramide orally disintegrating tablets).

The Applicant submitted a proposed MG and REMS for Reglan (metoclopramide tablets) Tablets on March 25, 2009. The REMS is currently under review by DRISK, and will be provided to 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 6.1, and a Flesch Reading Ease score of 68.8%. 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). The reading scores as submitted by the Applicant are acceptable.

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. In the section "What is Reglan?"
   - We have made the information about "What is Reglan?" consistent with the labeled indication. The applicant's use of the term (b) (4) seems too broad and implies that this product is used for all types of (b) (4)
   - We also clarified that the healing of ulcers refers to esophageal ulcers.
   - While the product is recommended for adults only, use in children is not a labeled contraindication. We have added a pediatric statement at the end of this section.
2. In the section "What are the possible side effects of Reglan?"
   - We incorporated language about Neuroleptic Malignant Syndrome similar to what was recently approved in the Zyprexa and Symbyax MGs.

- We re-ordered the symptoms for which patients should call their doctor or get medical help right away to reflect the fact that depression and thoughts of suicide, and symptoms of NMS are more urgent that TD and dystonia.
- The applicant should clarify how they chose the common side effects proposed in the MG. Only CNS side effects are listed. 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. We recommend that the review division address the common side effects consistently across all of the products in the class.

3. We have added the following statement to the end of the section, "What are the possible side effects of Reglan?":

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

   This verbatim statement is required for all Medication Guides.[1]

Please let us know if you have any questions.

[1] 21 CFR 208.20 (b)(7)(iii)

Medication Guide for

REGLAN® (REG-lan) Tablets

(metoclopramide tablets)

Read the Medication Guide that comes with REGLAN before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition (b) (4) (b) (4) or your treatment.

What is the most important information I should (b) (4) know about REGLAN?

REGLAN can cause serious side effects, including:

(b) (4) **Aabnormal muscle movements** called tardive dyskinesia (b) (4) (b) (4) (TD). These movements happen (b) mostly in the face muscles. You can not control these movements. They may not go away even after stopping REGLAN. There is no treatment for TD, but symptoms may lessen or go away over time.

Your chances for getting TD go up:

- the longer you take REGLAN and the more REGLAN you take. You (b) (4) should not take REGLAN for more than12 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 are will get TD if you take REGLAN.

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

(b) (4)

See the section "What are the possible side effects of REGLAN Tablets?" for more information about side effects.

What is REGLAN?

REGLAN is a prescription medicine used: *[DRISK Comment: We have made the information about "What is REGLAN?" consistent with the labeled indication. The applicant's use of the term* (b) (4) *seems too broad and implies that this product is used for all types of* (b) (4) *We have also clarified that the healing of ulcers refers to esophageal ulcers. While the product is recommended for adults only, use in children is not a labeled contraindication. We have added a pediatric statement at the end of this section.]*

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

(b) (4)

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

Who should not take REGLAN?

Do not take REGLAN if you:

- have stomach or intestine problems that could get worse with REGLAN, such as bleeding, blockage or a tear in the stomach or bowel wall
- have an adrenal gland -tumor called a pheochromocytoma (b) (4) (b) (4)
- are allergic to REGLAN or anything in it. (b) (4) (b) (4) See the end of this Medication Guide for a list of ingredients in REGLAN. (b) (4) (b) (4)
- take medicines that can cause uncontrolled movements, such as medicines for mental illness
- have seizures

(b) (4) *[DRISK Comment: A Pediatric statement has been added to the section "What is REGLAN? This placement is consistent with other Medication Guides.]*

What should I tell my doctor before taking REGLAN?

Tell your doctor about all your medical conditions (b) (4) 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. REGLAN 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 REGLAN will (b) (4) harm your (b) unborn baby.
- you are breast-feeding. REGLAN 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 REGLAN.

Tell your doctor about all the (b) (4) **medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.** (b) (4) (b) (4) (b) (4) REGLAN and some other medicines may interact with each other and may not work as well, or (b) cause possible side effects. Do not start any new medicines while taking REGLAN until you talk with your doctor. **Especially tell your doctor if you take:**

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

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

Know (b) (4) the medicines you take. Keep a list of them and (b) (4) show it to your doctor and (b) (4) pharmacist when you get a new medicine.

How should (b) (4) I take REGLAN?

- REGLAN comes as a tablet you take by mouth.

- Take REGLAN exactly as your doctor tells you. Do not change (b) (4) your dose (b) (4) unless your doctor tells you.
- (b) You should not take REGLAN for more than 12 weeks.
- If you take too much REGLAN, call your doctor or poison control center right away.

What should I avoid while taking REGLAN?

- Do not drink alcohol while taking REGLAN. Alcohol may make some side effects of REGLAN worse, such as (b) feeling sleepy. (b) (4)
- Do not drive, work with machines, or do dangerous tasks until you know how REGLAN affects you.

What are the possible side effects of REGLAN?

Reglan can cause serious side effects, including: (b) (4)

- Abnormal muscle movements. (b) (4) (b) (4) **See "What is the most important information I need to about know REGLAN?"**
- **Depression, ~~and~~ thoughts about suicide, and suicide**. Some people who take (b) (4) REGLAN becoame depressed. You may have (b) (4) thoughts about hurting or killing yourself. (b) (4) Some people who take Reglan have ended their own lives (suicide).
- Neuroleptic Malignant Syndrome (NMS). NMS is a very rare but very serious condition that can happen with Reglan. NMS can cause death and must be treated in a hospital. Symptoms of NMS include: h~~H~~igh fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating. *[DRISK Comment: We have made the language in this bullet similar to language about NMS that was recently approved in the Zyprexa and Symbyax MGs.]*

(b) (4)

- Uncontrolled spasms of your f~~F~~ace and neck muscles, or muscles of your (b) (4) body, arms, and legs (b) (4) (dystonia). These muscle spasms can cause abnormal movements and body positions (b) (4) These spasms usually start within the first 2 days of treatment.
- Parkinsonism. Symptoms include slight shaking, body stiffness, trouble moving or keeping your balance.

Call your doctor and get medical help (b) (4) 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
- hHave muscle movements you cannot stop or control
- hHave muscle movements that are new or unusualodd

(b) (4)

[DRISK Comment: We re-ordered the symptoms for which patients should call their doctor or get medical help right away to reflect the fact that depression and thoughts of suicide, and symptoms of NMS are more urgent than TD and dystonia.]

Common side effects of Reglan include:

- fFeeling restless, sleepy, tired, or dizzy, or exhausted
- hHeadache
- cConfusion
- tTrouble sleeping

[DRISK Comment: The applicant should clarify how they chose the common side effects proposed in the MG. Only CNS side effects are listed. 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.]

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

You may still have side effects after stopping REGLAN. You may have symptoms from stopping (b) (4) (b) (4) withdrawal) REGLAN -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 possibleThere are other side effects of REGLAN.

Call your doctor for medical advice about side effects. (b) (4) (b) (4) You may report side effects to (b) (4) (b) (4) (FDA) **at 1-800-FDA-1088.** *[DRISK Comment: This verbatim statement is required for all Medication Guides.]*

How should (b) (4) I store REGLAN?

- Keep (b) (4) REGLAN (b) (4) at room temperature between, 68°F to 77°F (20°C to 25°C).
- Keep REGLAN in the bottle it comes in. Keep the bottle closed tightly.

•Keep REGLAN and all medicines out of the reach of children.

General information about REGLAN

Medicines are (b) (4) sometimes prescribed for purposes other than (b) (4) those listed in a (b) Medication Guide.
•Do not use REGLAN for a condition (b) (4) for which it was not prescribed.
•Do not give REGLAN to other people (b) (4) even if they have the same symptoms that you have (b) (4) It may harm them.

This Medication Guide (b) (4) summarizes the most important information about REGLAN. If you would like more information, (b) (4)
•tTalk with your doctor. (b) (4)
•You can Aask your doctor or pharmacist for information about REGLAN that is written for health professionals. For more information, go to www.alavenpharma.com or
•cCall 1-888-317-0001.
(b) (4)

What are the ingredientsis in REGLAN?

Active ingredient: metoclopramide
Inactive ingredients:
REGLAN 10 mg tablets: magnesium stearate, mannitol, microcrystalline cellulose, stearic acid

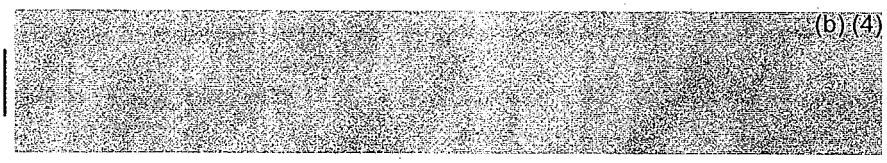
REGLAN 5 mg tablets: corn starch, D&C yellow 10 aluminum lake, FD&C blue 1 aluminum lake, lactose, microcrystalline cellulose, silicon dioxide, stearic acid

Manufactured for
Alaven Pharmaceutical LLC, Marietta, GA 30062

Revised Month Year

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

(b) (4)


(b) (4)

Medication Guide

REGLAN (REG-lan) Tablets
(metoclopramide tablets)

Read the Medication Guide that comes with REGLAN before you start taking it and each time you get a refill. There may be new information. 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 REGLAN?

REGLAN 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 REGLAN. There is no treatment for TD, but symptoms may lessen or go away over time.

Your chances for getting TD go up:

- the longer you take REGLAN and the more REGLAN you take. You should not take REGLAN for more than12 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 are will get TD if you take REGLAN.

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 REGLAN Tablets?" for more information about side effects.

What is REGLAN?

REGLAN is a prescription medicine used: *[DRISK Comment: We have made the information about "What is REGLAN?" consistent with the labeled indication. The applicant's use of the term* (b)(4) *seems too broad and implies that this product is used for all types of* (b)(4) *We have also clarified that the healing of ulcers*

refers to esophageal ulcers. While the product is recommended for adults only, use in children is not a labeled contraindication. We have added a pediatric statement at the end of this section.]

- **in adults for 4 to 12 weeks to relieve heartburn symptoms with gastroesophageal** reflux disease (GERD) when certain other treatments do not work. REGLAN 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. REGLAN helps treat symptoms such as nausea, vomiting, heartburn, feeling full long after a meal, and loss of appetite. Not all these symptoms get better at the same time.

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

Who should not take REGLAN?

Do not take REGLAN if you:
- have stomach or intestine problems that could get worse with REGLAN, such as bleeding, blockage or a tear in the stomach or bowel wall
- have an adrenal gland tumor called a pheochromocytoma
- are allergic to REGLAN or anything in it. See the end of this Medication Guide for a list of ingredients in REGLAN.
- take medicines that can cause uncontrolled movements, such as medicines for mental illness
- have seizures

[DRISK Comment: A Pediatric statement has been added to the section "What is REGLAN? This placement is consistent with other Medication Guides.]

What should I tell my doctor before taking REGLAN?

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. REGLAN 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 REGLAN will harm your unborn baby.

- you are breast-feeding. REGLAN 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 REGLAN.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. REGLAN 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 REGLAN until you talk with your doctor. **Especially tell your doctor if you take:**

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

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

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

How should I take REGLAN?

- REGLAN comes as a tablet you take by mouth.
- Take REGLAN exactly as your doctor tells you. Do not change your dose unless your doctor tells you.
- You should not take REGLAN for more than 12 weeks.
- If you take too much REGLAN, call your doctor or poison control center right away.

What should I avoid while taking REGLAN?

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

What are the possible side effects of REGLAN?

Reglan can cause serious side effects, including:

- **Abnormal muscle movements. See "What is the most important information I need to about know REGLAN?"**

- **Depression, thoughts about suicide, and suicide.** Some people who take REGLAN become depressed. You may have thoughts about hurting or killing yourself. Some people who take Reglan have ended their own lives (suicide).
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a very rare but very serious condition that can happen with Reglan. 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. ***[DRISK Comment: We have made the language in this bullet similar to language about NMS that was recently approved in the Zyprexa and Symbyax MGs.]***
- **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.
- **Parkinsonism.** Symptoms include slight shaking, body stiffness, trouble moving or keeping your balance.

Call your doctor and get medical help right away if you:
- feel depressed or have thoughts about hurting or killing yourself
- have high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating
- have muscle movements you cannot stop or control
- have muscle movements that are new or unusual

[DRISK Comment: We re-ordered the symptoms for which patients should call their doctor or get medical help right away to reflect the fact that depression and thoughts of suicide, and symptoms of NMS are more urgent than TD and dystonia.]

Common side effects of Reglan include:
- feeling restless, sleepy, tired, dizzy, or exhausted
- headache
- confusion
- trouble sleeping

[DRISK Comment: The applicant should clarify how they chose the common side effects proposed in the MG. Only CNS side effects are listed. 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.]

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

You may still have side effects after stopping REGLAN. You may have symptoms from stopping (withdrawal) REGLAN 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 REGLAN.

Call your doctor for medical advice about side effects. You may report side effects to **FDA at 1-800-FDA-1088.** *[DRISK Comment: This verbatim statement is required for all Medication Guides.]*

How should I store REGLAN?

- Keep REGLAN at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep REGLAN in the bottle it comes in. Keep the bottle closed tightly.

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

General information about REGLAN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REGLAN for a condition for which it was not prescribed. Do not give REGLAN 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 REGLAN. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about REGLAN that is written for health professionals. For more information, go to www.alavenpharma.com or call 1-888-317-0001.

What are the ingredients in REGLAN?

Active ingredient: metoclopramide
Inactive ingredients:

REGLAN 10 mg tablets: magnesium stearate, mannitol, microcrystalline cellulose, stearic acid

REGLAN 5 mg tablets: corn starch, D&C yellow 10 aluminum lake, FD&C blue 1 aluminum lake, lactose, microcrystalline cellulose, silicon dioxide, stearic acid

Manufactured for
Alaven Pharmaceutical LLC, Marietta, GA 30062

Revised Month Year

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

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
4/20/2009 04:17:01 PM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-854/S051

21-793/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-854/S-051
NDA 21-793/S-004

PRIOR APPROVAL SUPPLEMENT

Alaven Pharmaceuticals, LLC
Attention: Mary Alonso
Director, Quality Assurance and Regulatory Affairs
200 North Cobb Parkway, Suite 428
Marietta, GA 30062

Dear Ms. Alonso:

Please refer to your supplemental NDA 17-854/S-051 for Reglan (metoclopramide) Tablets and supplemental NDA 21-793/S-004 for Reglan ODT (metoclopramide) Orally Disintegrating Tablets submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA).

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 Reglan Tablets and Reglan ODT Orally Disintegrating Tablets to address the risk of tardive dyskinesia associated with the use of these products based on new safety information about this risk identified since the products were approved. You were directed to submit prior-approval supplements 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 statements detailing the reasons why such a change is not warranted.

On March 26, 2009, FDA received your prior approval supplement that contained your proposed safety related labeling changes, including the 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 April 17, 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 these supplements, NDA 17-854/S-051 and NDA 21-793/S-004, ends on June 24, 2009.

If you have questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Joyce Korvick
5/18/2009 10:52:21 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-854/S-051
NDA 21-793/S-004

PRIOR APPROVAL SUPPLEMENT

Alaven Pharmaceuticals, LLC
Attention: Mary Alonso
Director, Quality Assurance and Regulatory Affairs
2260 Northwest Parkway, Suite D
Marietta, GA 30067

Dear Ms. Alonso:

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

Name of Drug Products:	Reglan (metoclopramide) Tablets Reglan ODT (metoclopramide) Orally Disintegrating Tablets
NDA Numbers:	17-854/S-051 21-793/S-004
Date of supplements:	March 25, 2009
Date of receipt:	March 26, 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 Reglan Tablets and Reglan ODT Orally Disintegrating Tablets to address the risk of tardive dyskinesia associated with the use of these products based on new safety information about this risk identified since the products were approved. You were directed to submit prior-approval supplements 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 statements detailing the reasons why such a change is not warranted.

On March 26, 2009, FDA received your prior-approval supplements that contained your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplements 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 these supplements, NDA 17-854/S-051 and NDA 21-793/S-004, ends on May 25, 2009.

If you have questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Joyce Korvick
4/17/2009 12:40:05 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: May 6, 2009

To: Mary Alonso, Director of QA	**From:** Maureen Dewey
Company: Alaven Pharmaceuticals	Division of Gastroenterology Products
Fax number: 678-589-0500	**Fax number:** (301) 796-9905
Phone number: 678-589-7000	**Phone number:** (301) 796-0845

Subject: Agency proposed Labeling and Medication Guide for NDA 17-854 and NDA 21-793

Total no. of pages including cover:

Comments:

Ms. Alonso:,

Please see the enclosed proposed changes to the Reglan Tablet and Reglan ODT package insert and Medication Guide. Please review the changes proposed by the Agency and incorporate accordingly.

If possible, please respond to the proposed changes by **Tuesday, May 12, 2009** by sending a Word copy with your proposed Track Changes (if any) to Wes Ishihara (email: richard.ishihara@fda.hhs.gov).

A teleconference will be held to discuss any proposed changes on **Wednesday, May 13 at 3:00 PM.** Please feel free to contact Wes Ishihara at (301) 796-0069 if you have any questions.

Thank you, Maureen Dewey

Document to be mailed: **YES** ☑**NO**

8 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 17-854/505
21-763/004

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

/s/

Maureen Dewey
5/6/2009 03:04:20 PM
CSO

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
- ☐ 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 will be harmonized across the medication guides is the Boxed warning, and the Tardive Dyskinesia subsection under Warnings (this language is also provided in the supplement request letter sent to the sponsors). The REMS documents should also be fairly similar in that the REMS goal should be the same; however, sponsors may have different methods of distributing the medication guide. For the package insert, DGP requests only that DDMAC review the class language of the Boxed Warning and warnings section.

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

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

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

/s/

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES **Public Health Service**
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Regulatory Policy
Division of Information Disclosure Policy
10903 New Hampshire Avenue
Building 51, Room 6269
Silver Spring, Maryland 20993-0002

CERTIFICATE

Pursuant to the provisions of Rule 27 of the Federal Rules of Criminal Procedure and Rule 44 of the Federal Rules of Civil Procedure, I hereby certify that Tanya Higbee-Cerny, Regulatory Counsel, Division of Information Disclosure Policy, Center for Drug Evaluation and Research, whose Affidavit is attached, has custody of the records relating to human drugs on file with the United States Food and Drug Administration.

In witness whereof, I have, pursuant to the provisions of Title 42, United States Code, section 3505, and the authority delegated to me by the Commissioner of Food and Drugs, hereto set my hand and caused the seal of the Department of Health and Human Services to be affixed this 16th day of July, 2010.

Nancy B. Sager
Director
Division of Information Disclosure Policy
Center for Drug Evaluation and Research
By Direction of the Secretary of
Health and Human Services

DEPARTMENT OF HEALTH AND HUMAN SERVICES **Public Health Service**
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Regulatory Policy
Division of Information Disclosure Policy
10903 New Hampshire Avenue
Building 51, Room 6269
Silver Spring, Maryland 20993-0002

AFFIDAVIT

Tanya Higbee-Cerny, being duly sworn, deposes and says:

1. I am a Regulatory Counsel, Division of Information and Disclosure Policy, Center for Drug Evaluation and Research, United States Food and Drug Administration.

2. In this capacity I have custody of certain records relating to human drugs on file with the United Stated Food and Drug Administration.

3. Attached hereto is a true copy of NDA 17-854/S052 and NDA 21-793/S005. This document consists of 80 pages.

4. The document referred to in the above paragraph is part of the official records of the United States Food and Drug Administration.

Tanya Higbee-Cerny

State of Maryland)
County of Montgomery)

Subscribed and sworn to before me on this 16th day of July, 2010.

My commission expires 3/12/14.

Notary Public

CRYSTAL A. BUFFERT NOTARY PUBLIC MY COMMISSION EXPIRES MAR. 12, 2014 MONTGOMERY CO., MD

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

17-854/S052

21-793/S005

Trade Name: Reglan Tablets
Reglan Orally Disinegrating Tablets

Generic Name: (metoclopramide)

Sponsor: Alaven Pharmaceutical LLC

Approval Date: September 4, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-854/S052

21-793/S005

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Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
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Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL LETTER

17-854/S052
21-793/S005

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 017854/S-052
NDA 021793/S-005

APPROVAL LETTER

Alaven Pharmaceuticals, LLC
Attention: Mary Alonso
Director, Quality Assurance and Regulatory Affairs
200 North Cobb Parkway, Suite 428
Marietta, GA 30062

Dear Ms. Alonso:

Please refer to your supplemental NDA 17-854/S-051 for Reglan (metoclopramide) Tablets and supplemental NDA 21-793/S-004 for Reglan ODT (metoclopramide) Orally Disintegrating Tablets submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), dated March 25, 2009.

We acknowledge receipt of your submissions dated July 16, July 30, and August 6, 2009.

These supplemental new drug applications provide for a proposed Risk Evaluation and Mitigation Strategy (REMS) for Reglan (metoclopramide) Tablets and Reglan (metoclopramide) Orally Disintegrating Tablets as requested in our letter dated February 26, 2009.

We completed our review of these supplemental new drug applications, as amended. They are approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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

Reglan (metoclopramide) Tablets and Reglan ODT (metoclopramide) Orally Disintegrating Tablets were approved on December 30, 1980, and June 10, 2005, respectively. Current product labeling warns of the risk of tardive dyskinesia, a serious movement disorder, with chronic metoclopramide treatment. Tardive dyskinesia is often irreversible. Several risk factors, including female gender, advanced age, treatment duration and total cumulative dose have been described. Recently published analyses suggest that metoclopramide has surpassed haloperidol as the most common cause of drug-induced movement disorders. A published FDA analysis of metoclopramide utilization patterns showed that prescription claims for cumulative periods longer than 90 days were recorded for a substantial portion of patients in that study. In addition, we have become aware of

continued spontaneous reports to the FDA of tardive dyskinesia associated with metoclopramide use. Exposure greater than 12 weeks was evident in a majority of these reports. This information was not available when Reglan (metoclopramide) Tablets and Reglan ODT (metoclopramide) Orally Disintegrating Tablets were granted marketing authorization. We consider this information to be "new safety information" as defined in FDAAA.

Your proposed REMS, submitted on March 25, 2009, and amended on July 16, July 30, and August 6, 2009, is appended to this letter, and is approved. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

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

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

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

NDA 017854 or NDA 021793 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 017854 or NDA 021793
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 017854 or NDA 021793
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

PROMOTIONAL MATERIALS

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

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

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

LETTER TO HEALTHCARE PROFESSIONALS

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

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

REPORTING REQUIREMENTS

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

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

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

Enclosure: REMS documents

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-17854	SUPPL-52	ALAVEN PHARMACEUTICAL LLC	REGLAN

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

/s/

JOYCE A KORVICK
09/04/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-854/S052
21-793/S005

LABELING

Medication Guide

REGLAN (REG-lan) Tablets
(metoclopramide tablets)

Read the Medication Guide that comes with REGLAN 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 injection, REGLAN ODT, or metoclopramide oral syrup), 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 REGLAN?

REGLAN 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 REGLAN. There is no treatment for TD, but symptoms may lessen or go away over time after you stop taking REGLAN.

Your chances for getting TD go up:

- the longer you take REGLAN and the more REGLAN you take. You should not take REGLAN 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 REGLAN.

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 REGLAN?" for more information about side effects.

What is REGLAN?

REGLAN 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. REGLAN 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. REGLAN helps treat symptoms such as nausea, vomiting, heartburn, feeling full long after a meal, and loss of appetite. Not all these symptoms get better at the same time.

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

Who should not take REGLAN?

Do not take REGLAN if you:

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

What should I tell my doctor before taking REGLAN?

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. REGLAN 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 REGLAN will harm your unborn baby.
- you are breast-feeding. REGLAN 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 REGLAN.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. REGLAN 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 REGLAN until you talk with your doctor.

Especially tell your doctor if you take:

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

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

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

How should I take REGLAN?

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

What should I avoid while taking REGLAN?

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

What are the possible side effects of REGLAN?

Reglan can cause serious side effects, including:

- **Abnormal muscle movements.** See "What is the most important information I need to about know REGLAN?"

- **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 REGLAN become depressed. You may have thoughts about hurting or killing yourself. Some people who take Reglan have ended their own lives (suicide).
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a very rare but very serious condition that can happen with Reglan. 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 REGLAN.

Call your doctor and get medical help right away if you:
- feel depressed or have thoughts about hurting or killing yourself
- have high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating
- have muscle movements you cannot stop or control
- have muscle movements that are new or unusual

Common side effects of Reglan include:
- feeling restless, sleepy, tired, dizzy, or exhausted
- headache
- confusion
- trouble sleeping

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

You may still have side effects after stopping REGLAN. You may have symptoms from stopping (withdrawal) REGLAN 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 REGLAN.

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 REGLAN?
- Keep REGLAN at room temperature between 68°F to 77°F (20°C to 25°C).

- Keep REGLAN in the bottle it comes in. Keep the bottle closed tightly.

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

General information about REGLAN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REGLAN for a condition for which it was not prescribed. Do not give REGLAN 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 REGLAN. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about REGLAN that is written for health professionals. For more information, go to www.alavenpharma.com or call 1-888-317-0001.

What are the ingredients in REGLAN?

Active ingredient: metoclopramide
Inactive ingredients:

REGLAN 10 mg tablets: magnesium stearate, mannitol, microcrystalline cellulose, stearic acid

REGLAN 5 mg tablets: corn starch, D&C yellow 10 aluminum lake, FD&C blue 1 aluminum lake, lactose, microcrystalline cellulose, silicon dioxide, stearic acid

Manufactured for
Alaven Pharmaceutical LLC, Marietta, GA 30062

Revised June 2009

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

NDA 21-793 REGLAN ODT™

(metoclopramide orally disintegrating tablets)

Alaven Pharmaceutical, LLC
200 North Cobb Parkway, Suite 428
Marietta, GA 30062
Contact Information: Mary Alonso
Director of Quality Assurance and Regulatory Affairs

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

III. GOAL

The goal of this REMS is to minimize the risk of tardive dyskinesia associated with the long term use of REGLAN ODT™ (metoclopramide orally disintegrating tablets).

IV. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each REGLAN ODT prescription. REGLAN ODT is supplied as 5mg and 10 mg tablets (packaged in bottles of 100 tablets).

In accordance with 21 CFR 208.24, Alaven will package a sufficient number of Medication Guides with each container of drug product to ensure that a Medication Guide is available for distribution to patients. Four Medication Guides will be attached to each bottle. A tear pad of Medication Guides will also be provided to all US pharmacies that dispense REGLAN ODT.

The Medication Guide will be available for distribution to all patients with each prescription that is dispensed. Additional Medication Guides can be accessed from www.alavenpharm.com. Therefore, Alaven Pharmaceutical has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide. A reminder to provide the Medication Guide each time REGLAN ODT is dispensed will be printed on the bottle.

The Medication Guide is attached to this document as Appendix A.

B. Communication Plan

This REMS for REGLAN ODT does not include a Communication Plan.

C. Elements to Assure Safe Use

This REMS for REGLAN ODT can be approved without Elements to Assure Safe Use.

D. Implementation System

Because this REMS for REGLAN ODT can be approved without Elements to Assure Safe Use, an implementation system is not required.

E. Timetable for Submission of Assessments

REMS Assessments will be submitted to the FDA 18 months, 3 years and 7 years after approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before submission date for that assessment. Alaven will submit each assessment so that it will be received by the FDA on or before the due date.

Timetable for Submission of Assessments	
Assessment	Month/Year of Submission
1st Assessment (18 months from approval)	March 2011
2nd Assessment (3 years from approval)	September 2012
3rd Assessment (7 years from approval)	September 2016

Medication Guide

REGLAN ODT (REG-lan Oh-dee-tee) (metoclopramide orally disintegrating tablets)

Read the Medication Guide that comes with REGLAN ODT 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 injection, or metoclopramide oral syrup), 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 REGLAN ODT?

REGLAN ODT 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 REGLAN ODT. There is no treatment for TD, but symptoms may lessen or go away over time after you stop taking REGLAN ODT.

Your chances for getting TD go up:

- the longer you take REGLAN ODT and the more REGLAN ODT you take. You should not take REGLAN ODT 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 REGLAN ODT.

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 REGLAN ODT?" for more information about side effects.

What is REGLAN ODT?

REGLAN ODT 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. REGLAN ODT 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. REGLAN ODT helps treat symptoms such as nausea, vomiting, heartburn, feeling full long after a meal, and loss of appetite. Not all these symptoms get better at the same time.

It is not known if REGLAN ODT is safe and works in children.

Who should not take REGLAN ODT?

Do not take REGLAN ODT if you:

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

What should I tell my doctor before taking REGLAN ODT?

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. REGLAN ODT may cause your body to hold fluids.
- diabetes. Your dose of insulin may need to be changed.
- breast cancer
- phenylketonuria. REGLAN ODT contains aspartame.
- you are pregnant or plan to become pregnant. It is not known if REGLAN ODT will harm your unborn baby.
- you are breast-feeding. REGLAN ODT 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 REGLAN ODT.

Tell your doctor about all the medicines you take including, prescription and non-prescription medicines, vitamins, and herbal supplements. REGLAN ODT 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 REGLAN ODT until you talk with your doctor.

Especially tell your doctor if you take:

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

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

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

How should I take REGLAN ODT?

- REGLAN ODT comes as a tablet that melts in your mouth.
- Take REGLAN ODT exactly as your doctor tells you. Do not change your dose unless your doctor tells you.
- You should not take REGLAN ODT for more than 12 weeks.
- To take REGLAN ODT:
  - Leave the tablet in the bottle until you are ready to take it.
  - Use dry hands to take out a tablet. If your hands are wet, the tablets will melt.
  - Put the tablet on your tongue right away. Let it melt and then swallow. You do not need water to take REGLAN ODT.
- If you take too much REGLAN ODT, call your doctor or Poison Control Center right away.

What should I avoid while taking REGLAN ODT?

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

What are the possible side effects of REGLAN ODT?

Reglan ODT can cause serious side effects, including:

- **Abnormal muscle movements.** See "What is the most important information I should know about REGLAN ODT?"
- **Uncontrolled spasm 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 REGLAN ODT become depressed. You may have thoughts about hurting or killing yourself. Some people who take REGLAN ODT have ended their own lives (suicide).
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a rare but very serious condition that can happen with REGLAN ODT. 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 REGLAN ODT.

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 can not stop or control
- have muscle movements that are new or unusual

Common side effects include:

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

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

You may still have side effects after you stop REGLAN ODT. You may have symptoms from stopping (withdrawal) REGLAN ODT 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 REGLAN ODT.

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

How do I store REGLAN ODT?

- Keep REGLAN ODT at room temperature between 68°F to 77°F (20°C to 25°C).

- Keep REGLAN ODT in the bottle it comes in. Keep the bottle closed tightly.
- Keep REGLAN ODT dry so it does not melt.

Keep REGLAN ODT and all medicines out of the reach of children.

General information about REGLAN ODT

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REGLAN ODT for a condition for which it was not prescribed. Do not give REGLAN ODT 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 REGLAN ODT. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about REGLAN ODT that is written for health professionals. For more information go to www.alavenpharma.com or call 1-888-317-0001.

What are the ingredients in REGLAN ODT?

Active ingredient: metoclopramide

Inactive ingredients: aspartame, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, aminoalkyl methacrylate copolymer, microcrystalline cellulose, natural and artificial orange flavor, povidone

Manufactured for

Alaven Pharmaceutical LLC, Marietta, GA 30062

Revised June 2009
This Medication Guide has been approved by the U.S. Food and Drug Administration.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-854/S052

21-793/S005

REMS

NDA 17-854 REGLAN® tablets (metoclopramide tablets, USP)

Alaven Pharmaceutical, LLC
200 North Cobb Parkway, Suite 428
Marietta, GA 30062
Contact Information: Mary Alonso
Director of Quality Assurance and Regulatory Affairs

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is to minimize the risk of tardive dyskinesia associated with the long term use of REGLAN® tablets (metoclopramide tablets, USP).

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each REGLAN tablet prescription. REGLAN tablets are supplied as 5mg and 10 mg tablets (supplied in bottles of 100 tablets).

In accordance with 21 CFR 208.24, Alaven will package a sufficient number of Medication Guides with each container of drug product to ensure that a Medication Guide is available for distribution to patients. Four Medication Guides will be packaged within the plastic overwrapping for each bottle. A tear pad of Medication Guides will also be provided to all US pharmacies that dispense REGLAN tablets.

The Medication Guide will be available for distribution to all patients with each prescription that is dispensed. Additional Medication Guides can be accessed from

www.alavenpharm.com. Therefore, Alaven Pharmaceutical (the Sponsor) has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide. A reminder to provide the Medication Guide each time REGLAN tablets are dispensed will be printed on the bottle.

The Medication Guide is attached to this document as Appendix A.

B. Communication Plan

This REMS for REGLAN tablets does not include a Communication Plan.

C. Elements to Assure Safe Use

This REMS for REGLAN tablets can be approved without Elements to Assure Safe Use.

D. Implementation System

Because this REMS for REGLAN tablets can be approved without Elements to Assure Safe Use, an implementation system is not required.

E. Timetable for Submission of Assessments

REMS Assessments will be submitted to the FDA 18 months, 3 years and 7 years after approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission for that assessment.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-854/S052

21-793/S005

MEDICAL REVIEW(S)

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.

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

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)

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

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.

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)
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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.

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.

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.

Christopher Leptak, MD., PhD.,
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Tardive dyskinesia class-labeling for metoclopramide products

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.*

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.

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

/s/

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

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

[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.*"

---

[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

DIVISION OF GASTROENTEROLOGY PRODUCTS
MEDICAL OFFICER'S REVIEW

FDAAA SAFETY REVIEW OF REMS ELEMENTS FOR METOCLOPRAMIDE REFERENCE LISTED DRUGS

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

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

Purpose

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

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

Materials Reviewed

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

Background

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

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

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

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

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

REMS Review

I. Goal

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

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

II. REMS Elements

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

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

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

Conclusion

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

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

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/s/

TAMARA N JOHNSON
08/25/2009

NANCY C SNOW
08/26/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-854/S052

21-793/S005

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Date:	June 22, 2009
To:	Donna Griebel, MD, Director Division of Gastrointestinal Products (DGP)
Through:	Claudia Karwoski, Pharm.D., Director (Acting) Division of Risk Management (DRISK)
From:	Mary Dempsey, Risk Management Program Coordinator (DRISK)
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Reglan Tablets (metoclopramide hydrochloride) Reglan ODT (metoclopramide hydrochloride orally disintegrating tablets)
Application Type/Number:	NDA 17-854 NDA 21-793
Applicant/sponsor:	Alaven Pharmaceutical, LLC
OSE RCM #:	2009-604

1 INTRODUCTION

This memorandum is in response to a request by the DGP to review the proposed REMS for the innovator and generic metoclopramide products. The comments below reflect our review of the proposed REMS for Reglan tablets. Please send these comments to the sponsor and request the sponsor provide a response to these comments and questions within 2 weeks upon receipt. Please let us know if you would like a meeting to discuss before sending. DRISK's review of the draft Medication Guide was sent to DGP in a separate memorandum dated April 20 and April 21, 2009.

2 MATERIAL REVIEWED

- NDA 171-854 Reglan tables (metoclopramide tablets) SLC and REMS Notification Letter, dated February 26, 2009
- Alaven Pharmaceuticals proposed REMS for NDA 17-854 and NDA 21-793 submitted March 26, 2009

3 CONCLUSION/RECOMMENDATIONS

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

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

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

Comments to Alaven:

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

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

2. The Medication Guide distribution procedure is appears to be acceptable as long as the quantity you provide is sufficient for each "usual" or average dose. For example:
   - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.

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

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

4. The timetable for submission of assessments is acceptable. You may combine the REMS assessments of both of your products. If the timetable for submission of assessments differs for the two products, the REMS assessment should be submitted on the earlier date.

5. Please submit your detailed plan to evaluate patients' understanding about the safe use of metoclopramide at least 3 months before you plan to conduct the evaluation. The submission should include:

    - All methodology and instruments that will be used to evaluate patients' understanding about the safe use of metoclopramide. This should include, but not be limited to:
        - Sample size and confidence associated with that sample size
        - How the sample will be determined (selection criteria)
        - The expected number of patients to be surveyed
        - How the participants will be recruited
        - How and how often the surveys will be administered
        - Explain controls used to minimize bias
        - Explain controls used to compensate for the limitations associated with the methodology
    - The survey instruments (questionnaires and/or moderator's guide).
    - Any background information on testing survey questions and correlation to the messages in the Medication Guide.

6. Please see appended REMS proposals for NDA 21-793 and 17-854 for additional track changes corresponding to comments in this review.

NDA 17-854 REGLAN® tablets (metoclopramide tablets, USP)

Alaven Pharmaceutical, LLC
200 North Cobb Parkway, Suite 428
Marietta, GA 30062
Contact Information: Mary Alonso
Director of Quality Assurance and Regulatory Affairs

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is to minimize the risk of tardive dyskinesia associated with the long-term use of REGLAN® tablets (metoclopramide tablets, USP).

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each REGLAN tablet prescription. REGLAN tablets are supplied as 5mg and 10 mg tablets (supplied in bottles of 100 tablets).

In accordance with 21 CFR 208.24, Alaven will package a sufficient number of Medication Guides with each container of drug product to ensure that a Medication Guide is available for distribution to patients. Two Medication Guides will be packaged within the plastic overwrapping for each bottle. A tear pad of Medication Guides will also be provided to all US pharmacies that dispense REGLAN tablets.

The Medication Guide will be available for distribution to all patients with each prescription that is dispensed. Additional Medication Guides can be accessed from www.alavenpharm.com. Therefore, Alaven Pharmaceutical (the Sponsor) has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide. A reminder to provide the Medication Guide each time REGLAN tablets are dispensed will be printed on the bottle.

The Medication Guide is attached to this document as Appendix A.

B. Communication Plan

This REMS for REGLAN tablets does not include a Communication Plan.

C. Elements to Assure Safe Use

This REMS for REGLAN tablets can be approved without Elements to Assure Safe Use.

D. Implementation System

Because this REMS for REGLAN tablets can be approved without Elements to Assure Safe Use, an implementation system is not required.

E. Timetable for Submission of Assessments

REMS Assessments will be submitted to the FDA 18 months, 3 years and 7 years after approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

APPENDIX A

REGLAN® tablets (metoclopramide tablets, USP) Medication Guide

NDA 21-793 REGLAN ODT™

(metoclopramide orally disintegrating tablets)

Alaven Pharmaceutical, LLC

200 North Cobb Parkway, Suite 428

Marietta, GA 30062

Contact Information: Mary Alonso

Director of Quality Assurance and Regulatory Affairs

~~PROPOSED~~ RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is to minimize the risk of tardive dyskinesia associated with the long-term use of REGLAN ODT™ (metoclopramide orally disintegrating tablets).

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each REGLAN ODT prescription. REGLAN ODT is supplied as 5mg and 10 mg tablets (packaged in bottles of 100 tablets).

In accordance with 21 CFR 208.24, Alaven will package a sufficient number of Medication Guides with each container of drug product to ensure that a Medication Guide is available for distribution to patients. Two Medication Guides will be packaged within the plastic overwrapping for each bottle. A tear pad of Medication Guides will also be provided to all US pharmacies that dispense REGLAN ODT.

The Medication Guide will be available for distribution to all patients with each prescription that is dispensed. Additional Medication Guides can be accessed from www.alavenpharm.com. Therefore, Alaven Pharmaceutical has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide. A reminder to provide the Medication Guide each time REGLAN ODT is dispensed will be printed on the bottle.

The Medication Guide is attached to this document as Appendix A.

B. Communication Plan

This REMS for REGLAN ODT does not include a Communication Plan.

C. Elements to Assure Safe Use

This REMS for REGLAN ODT can be approved without Elements to Assure Safe Use.

D. Implementation System

Because this REMS for REGLAN ODT can be approved without Elements to Assure Safe Use, an implementation system is not required.

E. Timetable for Submission of Assessments

REMS Assessments will be submitted to the FDA 18 months, 3 years and 7 years after approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

APPENDIX A

REGLAN ODT™ (metoclopramide orally disintegrating tablets) Medication Guide

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/s/

Mary Dempsey
6/24/2009 11:19:37 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
6/24/2009 11:28:46 AM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-854/S052

21-793/S005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: May 6, 2009

To: Mary Alonso, Director of QA	**From:** Maureen Dewey
Company: Alaven Pharmaceuticals	Division of Gastroenterology Products
Fax number: 678-589-0500	**Fax number:** (301) 796-9905
Phone number: 678-589-7000	**Phone number:** (301) 796-0845

Subject: Agency proposed Labeling and Medication Guide for NDA 17-854 and NDA 21-793

Total no. of pages including cover:

Comments:

Ms. Alonso:,

Please see the enclosed proposed changes to the Reglan Tablet and Reglan ODT package insert and Medication Guide. Please review the changes proposed by the Agency and incorporate accordingly.

If possible, please respond to the proposed changes by **Tuesday, May 12, 2009** by sending a Word copy with your proposed Track Changes (if any) to Wes Ishihara (email: richard.ishihara@fda.hhs.gov).

A teleconference will be held to discuss any proposed changes on **Wednesday, May 13 at 3:00 PM.** Please feel free to contact Wes Ishihara at (301) 796-0069 if you have any questions.

Thank you, Maureen Dewey

Document to be mailed: **YES** ☑**NO**

8 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 17-854/5052
21-793/5005

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/s/

Maureen Dewey
5/6/2009 03:04:20 PM
CSO

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ NONCLINICAL

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

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

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

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

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

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

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

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

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

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

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/s/

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

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.

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

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

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

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

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/s/

Kristen Everett
4/3/2009 02:27:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-854/S-052
NDA 21-793/S-005

INFORMATION REQUEST LETTER

Alaven Pharmaceuticals, LLC
Attention: Mary Alonso
Director, Quality Assurance and Regulatory Affairs
200 North Cobb Parkway, Suite 428
Marietta, GA 30062

Dear Ms. Alonso:

Please refer to your new drug application NDA 17-854 for Reglan (metoclopramide) Tablets which was approved on December 30, 1980, and your NDA 21-793 for Reglan ODT (metoclopramide) Orally Disintegrating Tablets which was approved on June 10, 2005.

We also refer to your submissions dated March 25, 2009.

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

Goal of REMS

1. Revise your REMS goal as follows to be consistent with REMS goal for all metoclopramide products. [See attached REMS proposals with tracked changes.]

2. When you resubmit, delete the word "proposed".

Medication Guide

3. The Medication Guide distribution procedure appears to be acceptable as long as the quantity you provide is sufficient for each "usual" or average dose. For example:

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

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

Timetable for Submission of Assessments

5. The timetable for submission of assessments is acceptable. You may combine the REMS assessments of both of your products. If the timetable for submission of assessments differs for the two products, the REMS assessment should be submitted on the earlier date.

6. Please submit your detailed plan to evaluate patients' understanding about the safe use of metoclopramide at least 3 months before you plan to conduct the evaluation. The submission should include:

    - All methodology and instruments that will be used to evaluate patients' understanding about the safe use of metoclopramide. This should include, but not be limited to:
        - Sample size and confidence associated with that sample size
        - How the sample will be determined (selection criteria)
        - The expected number of patients to be surveyed
        - How the participants will be recruited
        - How and how often the surveys will be administered
        - Explain controls used to minimize bias
        - Explain controls used to compensate for the limitations associated with the methodology
    - The survey instruments (questionnaires and/or moderator's guide).
    - Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Please see appended REMS proposals for NDA 17-854 and NDA 21-793 for additional track changes corresponding to comments in this review. Submit the revised REMS with appended materials and documents by **July 20, 2009.** It is preferable that the entire REMS and appended materials be submitted as a single WORD document. If certain documents are only in PDF format, they may be submitted as such, but the preference is a single WORD document.

If you have any questions, please call Maureen Dewey, Regulatory Health Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Cristi L. Stark, M.S.
Acting Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 17-854 REGLAN® tablets (metoclopramide tablets, USP)

Alaven Pharmaceutical, LLC
200 North Cobb Parkway, Suite 428
Marietta, GA 30062
Contact Information: Mary Alonso
Director of Quality Assurance and Regulatory Affairs

~~PROPOSED~~ RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is to minimize the risk of tardive dyskinesia associated with the long-term use of REGLAN® tablets (metoclopramide tablets, USP).

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each REGLAN tablet prescription. REGLAN tablets are supplied as 5mg and 10 mg tablets (supplied in bottles of 100 tablets).

In accordance with 21 CFR 208.24, Alaven will package a sufficient number of Medication Guides with each container of drug product to ensure that a Medication Guide is available for distribution to patients. Two Medication Guides will be packaged within the plastic overwrapping for each bottle. A tear pad of Medication Guides will also be provided to all US pharmacies that dispense REGLAN tablets.

The Medication Guide will be available for distribution to all patients with each prescription that is dispensed. Additional Medication Guides can be accessed from www.alavenpharm.com. Therefore, Alaven Pharmaceutical (the Sponsor) has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide. A reminder to provide the Medication Guide each time REGLAN tablets are dispensed will be printed on the bottle.

The Medication Guide is attached to this document as Appendix A.

B. Communication Plan

This REMS for REGLAN tablets does not include a Communication Plan.

C. Elements to Assure Safe Use

This REMS for REGLAN tablets can be approved without Elements to Assure Safe Use.

D. Implementation System

Because this REMS for REGLAN tablets can be approved without Elements to Assure Safe Use, an implementation system is not required.

E. Timetable for Submission of Assessments

REMS Assessments will be submitted to the FDA 18 months, 3 years and 7 years after approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

NDA 21-793 REGLAN ODT™

(metoclopramide orally disintegrating tablets)

Alaven Pharmaceutical, LLC

200 North Cobb Parkway, Suite 428

Marietta, GA 30062

Contact Information: Mary Alonso

Director of Quality Assurance and Regulatory Affairs

~~PROPOSED~~ RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is to minimize the risk of tardive dyskinesia associated with the long-term use of REGLAN ODT™ (metoclopramide orally disintegrating tablets).

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each REGLAN ODT prescription. REGLAN ODT is supplied as 5mg and 10 mg tablets (packaged in bottles of 100 tablets).

In accordance with 21 CFR 208.24, Alaven will package a sufficient number of Medication Guides with each container of drug product to ensure that a Medication Guide is available for distribution to patients. Two Medication Guides will be packaged within the plastic overwrapping for each bottle. A tear pad of Medication Guides will also be provided to all US pharmacies that dispense REGLAN ODT.

The Medication Guide will be available for distribution to all patients with each prescription that is dispensed. Additional Medication Guides can be accessed from www.alavenpharm.com. Therefore, Alaven Pharmaceutical has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide. A reminder to provide the Medication Guide each time REGLAN ODT is dispensed will be printed on the bottle.

The Medication Guide is attached to this document as Appendix A.

B. Communication Plan

This REMS for REGLAN ODT does not include a Communication Plan.

C. Elements to Assure Safe Use

This REMS for REGLAN ODT can be approved without Elements to Assure Safe Use.

D. Implementation System

Because this REMS for REGLAN ODT can be approved without Elements to Assure Safe Use, an implementation system is not required.

E. Timetable for Submission of Assessments

REMS Assessments will be submitted to the FDA 18 months, 3 years and 7 years after approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

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/s/

Cristi Stark
7/7/2009 02:31:56 PM

Dewey, Maureen

From: Mary Alonso [malonso@alavenpharm.com]
Sent: Friday, September 04, 2009 1:29 PM
To: Dewey, Maureen
Subject: RE: NDA 17-854/S-052 and NDA 21-793/S-005 REMs submissions

Yes, we did receive the fax.

Thanks and have a great weekend,
Mary

From: Dewey, Maureen [mailto:Maureen.Dewey@fda.hhs.gov]
Sent: Friday, September 04, 2009 1:04 PM
To: Mary Alonso
Subject: RE: NDA 17-854/S-052 and NDA 21-793/S-005 REMs submissions

Faxed REMS Letters a minute ago, please confirm

From: Mary Alonso [mailto:malonso@alavenpharm.com]
Sent: Thursday, September 03, 2009 9:25 AM
To: Dewey, Maureen
Subject: NDA 17-854/S-052 and NDA 21-793/S-005 REMs submissions

Good Morning Maureen,

Just checking to see if you need anything else from Alaven in regards to the REMs submissions for Reglan?

Best regards,
Mary

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-17854	SUPPL-52	ALAVEN PHARMACEUTICAL LLC	REGLAN

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/s/

MAUREEN D DEWEY
09/04/2009