CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-821/S018

APPROVAL LETTER

MAR - 9 1999

NDA 17-854/S-039
NDA 17-862/S-042
NDA 18-821/S-018

Wyeth-Ayerst Laboratories
Attention: Nanette E. Holston
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Holston:

Please refer to your supplemental new drug applications dated September 8, 1998, received September 10, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reglan (metoclopramide) Tablets, Injection, and Syrup, respectively.

We note that these supplements were submitted as 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

These supplemental new drug applications provide for revision of both the oral products package insert, as well as the injection product insert to include "possible AV block" in the ADVERSE REACTIONS section, Cardiovascular subsection. The supplements were submitted in response to our July 5, 1998 letter, and your submissions stated the week of October 5, 1998 as the implementation date for the change.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package inserts submitted September 8, 1998). Accordingly, these supplemental applications are approved effective on the date of this letter.

We note that the ADMIXTURE COMPATIBILITIES section of the package inserts lists multiple electrolytes and drugs, by specific manufacturer, with which Reglan Injection is compatible. In a February 19, 1999 telephone conversation with Ms. Melodi McNeil, of this Division, Mr. John Seneca, of your firm, indicated that several electrolytes and drugs (Potassium Chloride, USP; Magnesium Sulfate, USP; Aminophylline, USP; Methylprednisolone Sodium Succinate, USP, and Calcium Gluconate, USP) have been deleted from the ADMIXTURE COMPATIBILITIES section of the inserts because they are no longer manufactured by ESI.

Please evaluate the compatibility of Reglan Injection with the drugs and electrolytes listed above, as well as the others listed in the ADMIXTURE COMPATIBILITES section, in general, rather than by specific manufacturer. Please provide this evaluation to us and consider whether revision of the insert to remove the names of specific manufacturers is warranted.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, contact Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/ 3-9-99 /S/ 3/9/99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-821/S018

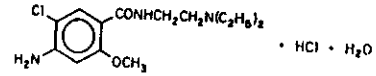
FINAL PRINTED LABELING

Reglan® Tablets
(Metoclopramide Tablets, USP)
Reglan® Syrup
(Metoclopramide Oral Solution, USP)
Reglan® Injectable
(Metoclopramide Injection, USP)

DESCRIPTION: For oral administration, Reglan Tablets (Metoclopramide Tablets, USP) 10 mg are white, scored, capsule-shaped tablets engraved Reglan on one side and AHR 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 AHR on the opposite side

Each tablet contains
Metoclopramide base ..... 5 mg
(as the monohydrochloride monohydrate)
Inactive Ingredients Corn Starch, D&C Yellow 10 Lake, FD&C Blue 1 Aluminum Lake, Lactose, Microcrystalline Cellulose, Silicon Dioxide, Stearic Acid
Reglan Syrup (Metoclopramide Oral Solution, USP) is an orange-colored, palatable, aromatic, sugar-free liquid
Each 5 mL (1 teaspoonful) contains.
Metoclopramide base ..... 5 mg
(as the monohydrochloride monohydrate)
Inactive Ingredients Citric Acid, FD&C Yellow 6, Flavors, Glycerin, Methylparaben, Propylparaben, Sorbitol, Water.
For parenteral administration, Reglan Injectable (Metoclopramide Injection, USP) is a clear, colorless, sterile solution with a pH of 4.5-6.5 for intravenous or intramuscular administration
CONTAINS NO PRESERVATIVE.

2 mL single dose vials/ampuls, 10 mL single dose vials; 30 mL single dose vials
Each 1 mL contains
Metoclopramide base ..... 5 mg
(as the monohydrochloride monohydrate)
Sodium Chloride, USP 8.5 mg, Water for Injection, USP q.s.
pH adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide
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. Molecular weight 354.3



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-ection, USP) is a clear, color-
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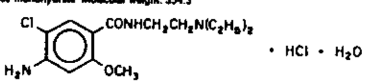
2 mL single dose vials/ampuls, 10 mL single dose vials; 30 mL single dose vials
Each 1 mL contains
Metoclopramide base . . . . 5 mg
(as the monohydrochloride monohydrate)
Sodium Chloride, USP 8.5 mg, Water for Injection, USP q.s.
pH adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide

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. Molecular weight: 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 1-2 hr after a single oral dose. Similar time to peak is observed after individual doses at steady state.

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In a single dose study of 12 subjects the area under the drug concentration-time curve increase 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 5-6 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

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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 cumulation

INDICATIONS AND USAGE: Symptomatic gastroesophageal reflux: Reglan Tablets and Syrup 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 (Metoclopramide Hydrochloride, 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.

The prevention of nausea and vomiting associated with emetogenic cancer chemotherapy. Reglan Injectable is indicated for the prophylaxis of vomiting associated with emetogenic cancer chemotherapy.

The prevention of postoperative nausea and vomiting. Reglan Injectable is indicated for the prophylaxis of postoperative nausea and vomiting in those circumstances where nasogastric suction is undesirable.

Small bowel intubation. Reglan Injectable may be used to facilitate small bowel intubation in adults and children in whom the tube does not pass the pylorus with conventional maneuvers.

Radiological examination. Reglan Injectable may be used to stimulate gastric emptying and intestinal transit of barium in cases where delayed emptying interferes with radiological examination of the stomach and/or small intestine.

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 30-40 mg/day of metoclopramide. These usually are seen during the first 24-48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and young adults, and are even more frequent at the higher doses used in prophylaxis of vomiting due to cancer chemotherapy. 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 Benadryl® (diphenhydramine hydrochloride) intramuscularly, and they usually will subside. Cogentin® (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

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...ating treatment with metoclopramide, but occasionally after longer periods. These symptoms ...ally subside within 2-3 months following discontinuance of metoclopramide. Patients with ...sisting Parkinson's disease should be given metoclopramide cautiously, if at all, since such ...patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

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

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

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

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.

Intravenous injections of undiluted metoclopramide should be made slowly allowing 1 to 2 minutes for 10 mg since a transient but intense feeling of anxiety and restlessness, followed by drowsiness, may occur with rapid administration.

Intravenous administration of Reglan injectable diluted in a parenteral solution should be made slowly over a period of not less than 15 minutes.

Giving a promotility drug such as metoclopramide theoretically could put increased pressure on sutures lines following a gut anastomosis or closure. Although adverse events related to this possibility have not been reported to date, the possibility should be considered and weighed when deciding whether to use metoclopramide or nasogastric suction in the prevention of postoperative nausea and vomiting.

Information for patients: 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.

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 exposure 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. There are insufficient data to support efficacy or make dosage recommendations for metoclopramide in patients less than 18 years of age except as stated to facilitate small bowel intubation (see **OVERDOSAGE** and **DOSAGE AND ADMINISTRATION**).

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. In cancer chemotherapy patients being treated with 1-2 mg/kg per dose, incidence of drowsiness is about 70%. 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. In cancer chemotherapy patients receiving 1-2 mg/kg per dose, the incidence is 2% in patients over the ages of 30-35, and 25% or higher in pediatric patients and young adults who have not had prophylactic administration of diphenhydramine. 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.

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, 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, especially with overdosage in neonates (see **OVERDOSAGE**).

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. 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. Transient flushing of the face and upper body, without alterations in vital signs, following high doses intravenously.

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.

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Unintentional overdose due to misadministration has been reported in patients between the ages of 2 months and 7 years with the use of Reglan syrup. 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 (1-4 mg/kg/day orally, intramuscularly or intravenously for 1-3 or more days). Methemoglobinemia has not been reported in neonates treated with 0.5 mg/kg/day in divided doses. Methemoglobinemia can be reversed by the intravenous administration of methylene blue.

DOSAGE AND ADMINISTRATION: 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 thus 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 Reglan Injectable (1 Ml or I.V.). Doses of 10 mg may be administered slowly by the intravenous route over a 1- to 2-minute period.

Administration of Reglan Injectable (Metoclopramide Injection, USP) 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.

For the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy: For doses in excess of 10 mg, Reglan Injectable should be diluted in 50 mL of a parenteral solution.

The preferred parenteral solution is Sodium Chloride Injection (normal saline), which when combined with Reglan Injectable, can be stored frozen for up to 4 weeks. Reglan Injectable is degraded when admixed and frozen with Dextrose-5% in Water. Reglan Injectable diluted in Sodium Chloride Injection, Dextrose-5% in Water, Dextrose-5% in 0.45% Sodium Chloride, Ringer's Injection or Lactated Ringer's Injection may be stored up to 48 hours (without freezing) after preparation if protected from light. All dilutions may be stored unprotected from light under normal light conditions up to 24 hours after preparation.

Intravenous infusions should be made slowly over a period of not less than 15 minutes, 30 minutes before beginning cancer chemotherapy and repeated every 2 hours for two doses, then 3 hours for three doses.

The initial two doses should be 2 mg/kg if highly emetogenic drugs such as cisplatin or dacarbazine are used alone or in combination. For less emetogenic regimens, 1 mg/kg per dose is adequate.

If extrapyramidal symptoms should occur, inject 50 mg Benadryl® (diphenhydramine hydrochloride) intramuscularly, and EPS usually will subside.

For the prevention of postoperative nausea and vomiting: Reglan Injectable should be given intramuscularly near the end of surgery. The usual adult dose is 10 mg, however, doses of 20 mg may be used.

To facilitate small bowel intubation: If the tube has not passed the pylorus with conventional

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maneuvers in 10 minutes, a single dose (undiluted) may be administered slowly by the intravenous route over a 1- to 2-minute period.

The recommended single dose is: Adults–10 mg metoclopramide base. Pediatric patients (6-14 years of age)–2.5 to 5 mg metoclopramide base, (under 6 years of age)–0.1 mg/kg metoclopramide base.

To aid in radiological examinations: In patients where delayed gastric emptying interferes with radiological examination of the stomach and/or small intestine, a single dose may be administered slowly by the intravenous route over a 1- to 2-minute period.

For dosage, see intubation above.

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.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

ADMIXTURE COMPATIBILITIES. Reglan Injectable (Metoclopramide Injection, USP) is compatible for mixing and injection with the following dosage forms to the extent indicated below.

Physically and Chemically Compatible up to 48 hours. Cimetidine Hydrochloride (SK&F), Mannitol, USP (Abbott), Potassium Acetate, USP (Invenex), Potassium Phosphate, USP (Invenex).

Physically Compatible up to 48 hours. Ascorbic Acid, USP (Abbott), Benztropine Mesylate, USP (MS&D), Cytarabine, USP (Upjohn), Dexamethasone Sodium Phosphate, USP (ESI, MS&D), Diphenhydramine Hydrochloride, USP (Parke-Davis), Doxorubicin Hydrochloride, USP (Adria), Heparin Sodium, USP (ESI), Hydrocortisone Sodium Phosphate (MS&D), Lidocaine Hydrochloride, USP (ESI), Multi-Vitamin Infusion (must be refrigerated-USV), Vitamin B Complex with Ascorbic Acid (Roche).

Physically Compatible up to 24 hours *(Do not use if precipitation occurs).* Clindamycin Phosphate, USP (Upjohn), Cyclophosphamide, USP (Mead-Johnson), Insulin, USP (Lilly).

Conditionally Compatible *(Use within one hour after mixing or may be infused directly into the same running IV line).* Ampicillin Sodium, USP (Bristol), Cisplatin (Bristol), Erythromycin Lactobionate, USP (Abbott), Methotrexate Sodium, USP (Lederle), Penicillin G Potassium, USP (Squibb), Tetracycline Hydrochloride, USP (Lederle).

Incompatible *(Do Not Mix).* Cephalothin Sodium, USP (Lilly), Chloramphenicol Sodium, USP (Parke-Davis), Sodium Bicarbonate, USP (Abbott).

HOW SUPPLIED: Each white, capsule-shaped, scored Reglan® Tablet contains 10 mg metoclopramide base (as the monohydrochloride monohydrate). Available in bottles of 100 (NDC 0031-6781-53), and 500 tablets (NDC 0031-6781-70) and Dis-Co® Unit Dose Packs of 100 tablets (NDC 0031-6781-64).

Each green, elliptical-shaped Reglan® Tablet contains 5 mg metoclopramide base (as the monohydrochloride monohydrate). Available in bottles of 100 (NDC 0031-6705-53) and Dis-Co® Unit Dose Packs of 100 tablets (NDC 0031-6705-64). Dispense tablets in tight, light-resistant container.

Reglan® Syrup, 5 mg metoclopramide base (as the monohydrochloride monohydrate) per 5 mL, available in pints (NDC 0031-6708-25). Dispense syrup in tight, light-resistant container.

PRESERVATIVE-FREE:

Reglan® Injectable 5 mg metoclopramide base (as the monohydrochloride monohydrate) per mL: available in 2 mL single dose vials in cartons of 25 (NDC 0031-6709-72), 10 mL single dose vials in cartons of 25 (NDC 0031-6709-78), 30 mL single dose vials in cartons of 25 (NDC 0031-6709-24), 2 mL ampuls in cartons of 25 (NDC 0031-6709-95).

- Tablet contains 5 mg metoclopramide base (as the mono-
...s in bottles of 100 (NDC 0031-6705-63) and Dis-Co® Unit
1 6705-64) Dispense tablets in tight, light-resistant

...ıl base (as the monohydrochloride monohydrate) per 5 mL,
25) Dispense syrup in tight, light-resistant container.

...amide base (as the monohydrochloride monohydrate) per mL;
...in cartons of 25 (NDC 0031-6709-72), 10 mL single dose
...6709-76), 30 mL single dose vials in cartons of 25
...ls in cartons of 25 (NDC 0031-6709-95)

Container	Total Contents #	Concentration #	Administration
2 mL single dose vial/ampul	10 mg	5 mg/mL	FOR IV or IM ADMINISTRATION
10 mL single dose vial	50 mg	5 mg/mL BEFORE USING	FOR IV INFUSION ONLY. DILUTE
30 mL single dose vial	150 mg	5 mg/mL	FOR IV INFUSION ONLY. DILUTE BEFORE USING

Metoclopramide base (as the monohydrochloride monohydrate)

Store vials and ampuls in carton until used. Do not store open single dose vials or ampuls for later use, as they contain no preservative.

Dilutions may be stored unprotected from light under normal light conditions up to 24 hours after preparation.

TABLETS, SYRUP AND INJECTABLE SHOULD BE STORED AT CONTROLLED ROOM TEMPERATURE, BETWEEN 20°C and 25°C (68°F and 77°F).

Reglan Injectable is manufactured for Pharmaceutical Division, A.H. Robins Company, Richmond, Virginia 23220 by Elkins-Sinn, Cherry Hill, NJ 08003, a division of A.H. Robins

CI 4803-3

Revised April 27, 1998

Printed in USA

A·H·ROBINS

Pharmaceutical Division
A.H. Robins Company, Richmond, VA 23220

Reglan® Tablets
(Metoclopramide Tablets, USP)
Reglan® Syrup
(Metoclopramide Oral Solution, USP)
Reglan® Injectable
(Metoclopramide Injection, USP)

CI 4803-3

DF

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Numbers and Name of Drug:

MAR - 9 1999

NDA 17-854/S-039; Reglan (metoclopramide) Tablets
NDA 17-862/S-042; Reglan (metoclopramide) Injection
NDA 18-821/S-018; Reglan (metoclopramide) Syrup

Sponsor: A.H. Robins

Material Reviewed

Submission Date(s): September 8, 1998, FPL

Receipt Date(s): September 10, 1998

Background and Summary Description: Reglan is approved in Tablet, Injection, and Syrup formulations for a variety of gastrointestinal disorders. There are two separate package inserts for these products. One is distributed with the oral products (Tablets and Syrup), and the other is distributed with the Injectable product. According to the firm, the inserts differ only in format (position of folds, bar codes, etc.); they are otherwise identical in content.

In a July 15, 1997 letter to the sponsor, the Division described the case of a 54-year old male patient who became asystolic five minutes after a dose of Reglan IV push. The firm was requested to analyze all available safety reports pertaining to compromised cardiac function, provide that analysis, and consider whether labeling revisions were warranted. In response to this request, NDAs 17-854/S-039, 17-862/S-042, and 18-821/S-018 were submitted as "Special Supplements – Changes Being Effected" in accordance with 21 CFR 314.70 (c) to provide for the addition of "possible AV block" to the ADVERSE REACTIONS section, Cardiovascular subsection of the package insert.

Note: The firm provided 1) the analysis requested in the July 15, 1997 letter and 2) copies of all referenced safety reports and literature reprints in support of this labeling change.

Review

Oral Insert:

The submitted insert (**coded CI 4803-3; Revised April 27, 1998**) was compared to the currently approved insert (**coded CI 4803-1; Issued December 14, 1995**, approved June 24, 1996 with NDAs [redacted]17-862/S-039, and 18-821/S-015). The following changes have been made:

1. DESCRIPTION section:

   This section has been modified as follows (throughout this review deletions are represented by strikeouts; added text is represented by a double underline):

   "2 mL~~[redacted]~~ single dose vials/ampuls; 10 mL single dose vials; 30 mL single dose vials"

   In a February 19, 1999 telephone conversation with Mr. John Seneca, Regulatory Affairs contact, he confirmed that the~~[redacted]~~l ampuls are no longer marketed. Therefore, this is an acceptable editorial revision.

2. ADVERSE REACTIONS section, Cardiovascular subsection:

   This section has been revised as follows: "Hypotension, hypertension, supraventricular tachycardia~~[redacted]~~bradycardia, and possible AV block (see CONTRAINDICATIONS and PRECAUTIONS)."

   According to Dr. Hugo Gallo-Torres, Medical Team Leader, the information submitted by the firm is sufficient to justify this change, therefore, this revision is acceptable.

3. ADMIXTURE COMPATABILITIES section:

   a. Physically And Chemically Compatible Up To 48 Hours subsection: "Potassium Chloride, USP (ESI)" has been deleted.

   b. Physically Compatible Up To 48 Hours subsection: "Magnesium Sulfate, USP (ESI)" has been deleted.

   c. Physically Compatible Up To 24 Hours subsection: "Aminophylline, USP (ESI)" and "Methylprednisolone Sodium Succinate, USP (ESI)" have been deleted.

   d. Conditionally Compatible subsection: "Calcium Gluconate, USP (ESI)" has been deleted.

   In a February 19, 1999 telephone conversation with Mr. John Seneca, Regulatory Affairs contact, he clarified that these electrolytes have been deleted from the package insert because they are no longer manufactured by ESI. According to Dr. Lilia Talarico, Division Director, these editorial revisions are acceptable, however, the firm should be requested to evaluate the compatibility of Reglan

Injectable with the electrolytes and drugs listed above (as well as the others listed in this section) in general, not just for certain manufacturers.

4. HOW SUPPLIED section:

   a. The portion which describes Reglan Injection has been revised as follows: "Reglan® Injectable 5 mg metoclopramide base (as the monohydrochloride monohydrate) per mL; available in 2 mL single dose vials in cartons of 25 (NDA 0031-6709-72), 10 mL single dose vials in cartons of 25 (NDC 0031-6709-78), 30 mL single dose vials in cartons of 25 (NDC 0031-6709-24), 2 mL ampuls in cartons of 25 (NDA 0031-6709-95)

   b. In addition, reference to the ampul has been deleted from the table summarizing the available container sizes for Reglan Injection.

   The Agency was notified that the were deleted from the HOW SUPPLIED section of the package insert in annual report –026 (Y-026) submitted to the Reglan Injection NDA (17-862) on May 1, 1998. In a February 19, 1999 telephone conversation, Mr. John Seneca, Regulatory Affairs contact, clarified that the deletions were made because these package configurations are no longer marketed. Therefore, this is an acceptable editorial revision.

5. Manufacturer/Distributor block:

   This section has been revised as follows: "Reglan Injectable is manufactured for Pharmaceutical Division, A.H. Robins Company, Richmond, Virginia 23220 by Elkins-Sinn, Cherry Hill, NJ 08003, a division of A.H. Robins.

   This is an acceptable editorial revision.

6. Overall:

   The firm has made numerous minor editorial and formatting changes which do not affect the meaning of the information that is presented. such as:

   a. All section headings have been revised from bold type, initial capital letters only to bold type, all capital letters (e.g., "**How Supplied**" to "**HOW SUPPLIED**").

   b. All subsection headings have been revised from regular type, all capital letters to bold

type, initial capital letters only (e.g., "DRUG INTERACTIONS" to "**Drug Interactions**").

c. The storage statement has been revised from regular to bold type.

These are acceptable editorial revisions.

IV Insert:

The submitted i.v. insert **(coded CI 4804-2; Revised July 2, 1998)** was compared to the submitted oral insert. They are identical in content.

Conclusions

The package inserts are acceptable as submitted and can be considered the currently approved labeling. The firm should be sent an Approval letter. However, as indicated above, the firm should also be requested to evaluate the compatibility of Reglan Injectable with the drugs and electrolytes specified in the ADMIXTURE COMPATIBILITIES section, as well as the ones that were editorially deleted, in general, not just for certain manufacturers.

/S/ 3/9/99
Regulatory Health Project Manager

/S/ 3-9-99

cc:
Original NDAs 17-854/S-039, 17-862/S-042, and 18-821
HFD-180/Div. Files
HFD-180/McNeil
HFD-180/Duffy
HF-2/Kennedy

draft: MMcNeil/February 18, 1999
r/d Initials: LTalarico 2/22/99
final: March 9, 1999

CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL