

**LACHMAN CONSULTANT SERVICES, INC.**  
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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September 7, 2004

**OVERNIGHT COURIER 9/7/04**

Division of Dockets Management  
Food and Drug Administration (HFA-305)  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Citizen Petition**

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Metoclopramide Hydrochloride Orally Disintegrating Tablets 5 mg and 10 mg, is suitable for consideration in an abbreviated new drug application (ANDA).

**A. Action Requested**

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Metoclopramide Hydrochloride Orally Disintegrating Tablets 5 mg and 10 mg are suitable for submission in an ANDA. The listed reference drug product upon which this petition is based is Reglan® (metoclopramide hydrochloride) Tablets 10 mg. (It is noted that Reglan® Tablets are also approved in a 5 mg strength. In addition, the FDA has previously approved a liquid version of Reglan®, however, this product is not currently being marketed.) The petitioner thus seeks a change in dosage form (from an immediate-release tablet to an orally disintegrating tablet) from that of the listed drug product.

**B. Statement of Grounds**

The reference-listed drug (RLD) product, Reglan® approved in NDA 17-854, is currently available in immediate-release tablet strengths of 5 mg and 10 mg tablets containing metoclopramide hydrochloride. A copy of the listing from the *Approved Drug Product with Therapeutic Equivalence Evaluations* 24<sup>th</sup> edition is included in Attachment 1 (page 3-246). The proposed drug product represents an orally disintegrating tablet that will contain the same strengths of the RLD (5 mg and 10 mg), but in a different dosage form.

The proposed orally disintegrating tablet is designed to provide for ease of administration for patients who cannot or who find it difficult to swallow immediate-release tablets. The product is designed to be dissolved rapidly on the tongue and swallowed without the need for water. The new proposed dosage form will provide a more convenient dosage form for those patients identified above and for those patients who are elderly and infirm and find it difficult to swallow a tablet or are not in a position to have water available when dosing is necessary. It will also provide the option of taking the medication without having to wash the tablet down with water, which based on the symptomatology of the approved indications, may be beneficial to certain patients.

Copies of labeling of the reference listed drug product upon which this petition is based and draft labeling for the proposed product are included in Attachment 2 and Attachment 3, respectively. Please note that the draft labeling for the proposed product will be revised to include the inactive ingredients and a complete "How Supplied" section when the ANDA is submitted. The proposed labeling is the "same as" the approved RLD labeling with the exception of changes allowed because the manufacturer of the generic product differs from that of the RLD and in regard to those changes necessary due to the approval of this petition (i.e., method of dosing [the ability to dissolve the tablet on the tongue]). There are no changes in the indications, uses or dosing regimen of the proposed product. The ANDA applicant will demonstrate that the proposed orally disintegrating tablet is bioequivalent to the RLD.

### **Pediatric Waiver Request**

In December of 2003, Congress passed the Pediatric Research Equity Act of 2003 that amended the Federal Food, Drug and Cosmetic Act to provide the Agency authority to require drug firms to study certain drugs in pediatric patients, if the Agency felt that such study would provide beneficial health data for that patient population. The act also provides a provision for a waiver from such requirement if:

(iii) the drug or biological product,

(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and

(II) is not likely to be used in a substantial number of pediatric patients.

The petitioner hereby requests that a waiver from the conduct of pediatric studies be granted for the approval of this petition to permit a subsequent ANDA filing.

Metoclopramide hydrochloride does not appear on the historical List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population.<sup>1</sup> While the RLD is available in an immediate-release tablet dosage form, it was additionally approved by the Agency in a liquid dosage form (Reglan®, NDA 18-821) in a strength of 5 mg / 5 mL. Despite the availability of an oral liquid dosage form, both the immediate-release tablets and oral solution have a clear warning against the use of the drug products in the pediatric patient due to the more frequent occurrence of extrapyramidal symptoms and other significant side effects. The labeling of the RLD states:

"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." (emphasis added)

In addition, the labeling states that:

"The use of Reglan® is recommended for adults only."

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<sup>1</sup> The list was accessed on September 1, 2004 from the following web address  
<http://www.fda.gov/cder/pediatric/peddrugsfinal.htm>

It is postulated that the severity and potential for adverse events with the use of metoclopramide in pediatric patients where other remedies and treatments are available, make it unwise to utilize this product in pediatric patients. Based on the use and nature of the RLD, the proposed change in dosage form from an immediate-release tablet to an orally disintegrating tablet will not likely make the product any more likely to be used in pediatric patients. In addition, the limitations of use (adults only) described in the labeling of the RLD, make it unlikely that the proposed product would be used in a substantial number of pediatric patients.

Additionally, for the associated indications there are other, safer alternatives for pediatric patients e.g., for the treatment of gastroesophageal reflux, and thus, the proposed product does not represent a meaningful therapeutic benefit over other existing therapies.

For the reasons cited above, the petitioner requests that the Commissioner find that a change in dosage form from an immediate-release tablet to an orally disintegrating tablet containing metoclopramide hydrochloride 5 mg and 10 mg raises no questions of safety or effectiveness, and the Agency should then approve the petition.

**C. Environmental Impact**

The petitioner claims a categorical exclusion under 21 CFR 25.31.

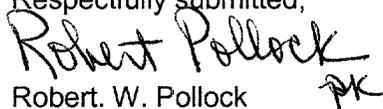
**D. Economic Impact**

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

**E. Certification**

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

  
pk

Robert. W. Pollock  
Vice President  
Lachman Consultant Services, Inc.  
1600 Stewart Avenue  
Westbury, New York 11590

RWP/pk

- Attachments:
1. Page 3-246 of the *Approved Drug Product with Therapeutic Equivalence Evaluations* 24<sup>th</sup> Edition
  2. Copy of Labeling of the Reference-listed Drug Product
  3. Draft Labeling for the Proposed Product

cc: Emily Thomas (OGD)

A31P4251

LACHMAN CONSULTANT SERVICES, INC.  
Westbury, NY 11590

**ATTACHMENT 1**

PRESCRIPTION DRUG PRODUCT LIST

3-246

METOCLOPRAMIDE HYDROCHLORIDE

SOLUTION; ORAL  
METOCLOPRAMIDE  
AA VISTAPHARM EQ 5MG BASE/5ML N75051 001  
 JAN 26, 2001  
AA METOCLOPRAMIDE HCL  
 ALPHARMA EQ 5MG BASE/5ML N71340 001  
 AUG 18, 1988  
AA PHARM ASSOC EQ 5MG BASE/5ML N72744 001  
 MAY 28, 1991  
AA PHARM VENTURES EQ 5MG BASE/5ML N71402 001  
 JUN 25, 1993  
AA ROXANE EQ 5MG BASE/5ML N72038 001  
 DEC 05, 1988  
AA SILARX EQ 5MG BASE/5ML N73680 001  
 OCT 27, 1992  
AA + TEVA EQ 5MG BASE/5ML N70819 001  
 JUL 10, 1987  
AA EQ 5MG BASE/5ML N71315 001  
 JUN 30, 1993

TABLET; ORAL  
METOCLOPRAMIDE HCL  
AB PLIVA EQ 5MG BASE N72750 001  
 DEC 28, 1995  
AB EQ 10MG BASE N71250 001  
 FEB 03, 1988  
AB PUREPAC PHARM EQ 10MG BASE N70581 001  
 OCT 17, 1985  
AB SANDOZ EQ 5MG BASE N74478 001  
 OCT 05, 1995  
AB EQ 10MG BASE N72215 001  
 JAN 30, 1990  
AB EQ 10MG BASE N74478 002  
 OCT 05, 1995  
AB TEVA EQ 5MG BASE N72801 001  
 JUN 15, 1993  
AB EQ 10MG BASE N70184 001  
 JUL 29, 1985  
AB WATSON LABS EQ 10MG BASE N70511 001  
 JAN 22, 1986  
AB REGLAN  
 SCHWARZ PHARMA EQ 5MG BASE N17854 002  
 MAY 05, 1987  
AB + EQ 10MG BASE N17854 001

METOLAZONE

TABLET; ORAL  
METOLAZONE  
AB EON 2.5MG N76732 001  
 DEC 19, 2003  
AB 5MG N76466 001  
 DEC 19, 2003  
AB 10MG N76466 002  
 DEC 19, 2003  
AB MYLAN 2.5MG N76698 001  
 DEC 23, 2003  
AB TEVA 10MG N75543 003  
 DEC 24, 2003  
 MYKROX  
 + CELLTECH PHARMS 0.5MG N19532 001  
 OCT 30, 1987  
ZAROXOLYN  
AB CELLTECH PHARMS 2.5MG N17386 001  
AB + 5MG N17386 002  
AB + 10MG N17386 003

METOPROLOL SUCCINATE

TABLET, EXTENDED RELEASE; ORAL  
 TOPROL-XL  
 ASTRAZENECA EQ 25MG TARTRATE N19962 004  
 FEB 05, 2001  
 + EQ 50MG TARTRATE N19962 001  
 JAN 10, 1992  
 EQ 100MG TARTRATE N19962 002  
 JAN 10, 1992  
 + EQ 200MG TARTRATE N19962 003  
 JAN 10, 1992

METOPROLOL TARTRATE

INJECTABLE; INJECTION  
LOPRESSOR  
AP + NOVARTIS 1MG/ML N18704 001  
 MAR 30, 1984  
METOPROLOL TARTRATE  
AP ABBOTT 1MG/ML N74133 001  
 DEC 21, 1993  
AP 1MG/ML N75160 001  
 JUL 06, 1998

LACHMAN CONSULTANT SERVICES, INC.  
Westbury, NY 11590

## ATTACHMENT 2

**reglan® tablets**

(metoclopramide tablets, USP)

PC4445D Rev. 02/04

Rx only

**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.

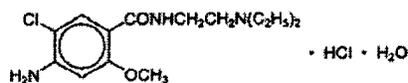
Each tablet contains:

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-5chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its molecular formula is C<sub>14</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>2</sub>•HCl•H<sub>2</sub>O. 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  $80\% \pm 15.5\%$  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.

<b>Adult Pharmacokinetic Data</b>	
<b>Parameter</b>	<b>Value</b>
Vd (L/kg)	~ 3.5
Plasma Protein Binding	~ 30%
t <sub>1/2</sub> (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<sup>®</sup> tablets is recommended for adults only. Therapy should not exceed 12 weeks in duration.

### **Symptomatic Gastroesophageal Reflux**

reglan<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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**

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

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

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

### **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<sup>®</sup>. A small number of patients may experience a withdrawal period after stopping reglan<sup>®</sup> that could include dizziness, nervousness, and/or headaches.

### **Information for Patients**

The use of reglan<sup>®</sup> 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.

### **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<sub>5</sub> 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<sup>®</sup> 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<sup>®</sup> that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving reglan<sup>®</sup>, reglan<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sub>5</sub> 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<sup>®</sup> tablets should not exceed 12 weeks in duration.

##### **For the Relief of Symptomatic Gastroesophageal Reflux**

Administer from 10 mg to 15 mg reglan<sup>®</sup> (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<sup>®</sup> 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<sup>®</sup> therapy should be reinstated 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<sup>®</sup> tablet (metoclopramide tablets, USP) contains 10 mg metoclopramide base (as the monohydrochloride monohydrate). Available in:

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

Bottles of 500 tablets (NDC 0091-6701-70)

Each green, elliptical-shaped reglan<sup>®</sup> 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**  
**P H A R M A**  
Milwaukee, WI 53201, USA

**ATTACHMENT 3**

## Metoclopramide Orally Disintegrating Tablets

(metoclopramide tablets, USP)

Rx only

### DESCRIPTION

For oral administration, metoclopramide orally disintegrating tablets (metoclopramide tablets, USP) 10 mg.

Each tablet contains:

Metoclopramide base .....10 mg  
(as the monohydrochloride monohydrate)

### Inactive Ingredients

This information will be provided when the ANDA is submitted.

Metoclopramide orally disintegrating tablets (metoclopramide tablets, USP) 5 mg.

Each tablet contains:

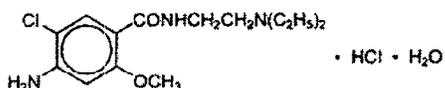
Metoclopramide base .....5 mg  
(as the monohydrochloride monohydrate)

### Inactive Ingredients

This information will be provided when the ANDA is submitted.

Metoclopramide hydrochloride is a white crystalline, odorless substance, freely soluble in water.

Chemically, it is 4-amino-5chloro-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  $80\% \pm 15.5\%$  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**

<b><u>Parameter</u></b>	<b><u>Value</u></b>
Vd (L/kg)	~ 3.5
Plasma Protein Binding	~ 30%
t <sub>1/2</sub> (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 metoclopramide orally disintegrating tablets is recommended for adults only. Therapy should not exceed 12 weeks in duration.**

##### **Symptomatic Gastroesophageal Reflux**

metoclopramide orally disintegrating 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)**

metoclopramide orally disintegrating 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 metoclopramide orally disintegrating 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. Benzotropine 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**

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

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

There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn.

Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the longterm course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.

### **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 metoclopramide orally disintegrating . A small number of patients may experience a withdrawal period after stopping metoclopramide orally disintegrating that could include dizziness, nervousness, and/or headaches.

#### **Information for Patients**

The use of metoclopramide 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.

#### **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 b5 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 orally disintegrating tablets 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 metoclopramide orally disintegrating that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving metoclopramide orally disintegrating, metoclopramide orally disintegrating 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 orally disintegrating tablet 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 orally disintegrating tablets are 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 b5 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. Porphyrria.

#### **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 metoclopramide orally disintegrating tablets should not exceed 12 weeks in duration.**

##### **For the Relief of Symptomatic Gastroesophageal Reflux**

Administer from 10 mg to 15 mg metoclopramide orally disintegrating tablets (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. Metoclopramide orally disintegrating tablets may be dissolved on the tongue and swallowed.

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 metoclopramide orally disintegrating 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, metoclopramide orally disintegrating tablet therapy should be reinstated 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**

This information will be provided when the ANDA is submitted.

**Dispense tablets in tight, light-resistant container.**

Tablets should be stored at controlled room temperature.