

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-793

LABELING

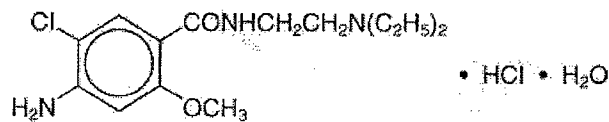
TRADENAME

(metoclopramide orally disintegrating tablets)

Rx Only**DESCRIPTION**

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

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



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

CLINICAL PHARMACOLOGY

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

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

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

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by

agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare (see **WARNINGS**). Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

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

Pharmacokinetics

Metoclopramide is rapidly and well absorbed. Relative to an intravenous dose of 20 mg, the absolute oral bioavailability of metoclopramide is $80\% \pm 15.5\%$ 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 mean elimination half-life of metoclopramide is approximately 7 hr after administration of TRADENAME. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

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

The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues. Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life. The kinetics of metoclopramide in the presence of renal impairment remained linear however. The reduction in clearance as a result of renal impairment suggests that adjustment downward of maintenance dosage should be done to avoid drug accumulation.

Adult Pharmacokinetic Data

Parameter	Value
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Vd (L/kg)	~ 3.5
Plasma Protein Binding	~ 30%
t _{1/2} (hr)	~ 7
Oral Bioavailability	80% ± 15.5%

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

There are insufficient reliable data to conclude whether the pharmacokinetics of metoclopramide in adults and the pediatric population are similar. Although there are insufficient data to support the efficacy of metoclopramide in pediatric patients with symptomatic gastroesophageal reflux (GER) or cancer chemotherapy-related nausea and vomiting, its pharmacokinetics have been studied in these patient populations.

In an open-label study, six pediatric patients (age range, 3.5 weeks to 5.4 months) with GER received metoclopramide 0.15 mg/kg oral solution every 6 hours for 10 doses. The mean peak plasma concentration of metoclopramide after the tenth dose was 2-fold (56.8 µg/L) higher compared to that observed after the first dose (29 µg/L) indicating drug accumulation with repeated dosing. After the tenth dose, the mean time to reach peak concentrations (2.2 hr), half-life (4.1 hr), clearance (0.67 L/h/kg), and volume of distribution (4.4 L/kg) of metoclopramide were similar to those observed after the first dose. In the youngest patient (age, 3.5 weeks), metoclopramide half-life after the first and the tenth dose (23.1 and 10.3 hr, respectively) was significantly longer compared to other infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at birth. Single intravenous doses of metoclopramide 0.22 to 0.46 mg/kg (mean, 0.35 mg/kg) were administered over 5 minutes to 9 pediatric cancer patients receiving chemotherapy (mean age, 11.7 years; range, 7 to 14 yr) for prophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time zero ranged from 65 to 395 µg/L (mean, 152 µg/L). The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.4 hr (range, 1.7 to 8.3 hr), 0.56 L/h/kg (range, 0.12 to 1.20 L/h/kg), and 3.0 L/kg (range, 1.0 to 4.8 L/kg), respectively.

In another study, nine pediatric cancer patients (age range, 1 to 9 yr) received 4 to 5 intravenous infusions (over 30 minutes) of metoclopramide at a dose of 2 mg/kg to control emesis. After the last dose, the peak serum concentrations of metoclopramide ranged from 1060 to 5680 µg/L. The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5 hr (range, 2.0 to 12.5 hr), 0.37 L/h/kg (range, 0.10 to 1.24 L/h/kg), and 1.93 L/kg (range, 0.95 to 5.50 L/kg), respectively.

INDICATIONS AND USAGE

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

Symptomatic Gastroesophageal Reflux

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

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

Diabetic Gastroparesis (Diabetic Gastric Stasis)

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

CONTRAINDICATIONS

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

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

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

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

WARNINGS

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

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30 to 40 mg/day of metoclopramide. These usually are seen during the first 24 to 48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less than 30 years of age and are even more frequent at higher doses. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm. If these symptoms should occur, inject 50 mg diphenhydramine hydrochloride intramuscularly, and they usually will subside. Benztropine mesylate, 1 to 2 mg intramuscularly, may also be used to reverse these reactions.

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

Tardive Dyskinesia

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 TRADENAME. A small number of patients may experience a withdrawal period after stopping TRADENAME that could include dizziness, nervousness, and/or headaches.

Information for Patients

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

The use of TRADENAME 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.

Phenylketonurics

Phenylketonuric patients should be informed that TRADENAME contains phenylalanine 4.2 mg per 5 mg orally disintegrating tablet and 8.3 mg per 10 mg orally disintegrating tablet.

Drug Interactions

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 77-week study was conducted in rats with oral doses of metoclopramide up to 40 mg/kg/day (about 5 times the maximum recommended human dose on surface area basis). Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments

indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

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

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

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

Pregnancy. Teratogenic Effects: Pregnancy Category B.

Teratology studies have been performed in rats at oral doses up to 45 mg/kg/day (about 6 times the maximum recommended human dose on surface area basis) and in rabbits at oral doses up to 45 mg/kg/day (about 12 times the maximum recommended human dose on surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother. Because of the potential for serious adverse reactions in nursing infants from metoclopramide and because of the potential for tumorigenicity and tumor promoting potential shown for metoclopramide in rats, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

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

Care should be exercised in administering metoclopramide to neonates since prolonged clearance may produce excessive serum concentrations (see **CLINICAL PHARMACOLOGY—Pharmacokinetics**). In addition, neonates have reduced levels of NADH-cytochrome 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 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 TRADENAME that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving TRADENAME, TRADENAME should generally be discontinued before initiating any specific anti-parkinsonian agents (see **WARNINGS** and **DOSAGE AND ADMINISTRATION – For the Relief of Symptomatic Gastroesophageal Reflux**).

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

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

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

For these reasons, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, concomitant disease, or other drug therapy in the elderly (see **DOSAGE AND ADMINISTRATION – For the Relief of Symptomatic Gastroesophageal Reflux and Use in Patients with Renal or Hepatic Impairment**).

Other Special Populations

Patients with NADH-cytochrome 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 four times daily (see **PRECAUTIONS**). Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation (see **WARNINGS**) occur less frequently. The incidence of drowsiness is greater at higher doses. There are isolated reports of

convulsive seizures without 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.

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

OVERDOSAGE

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

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

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

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

DOSAGE AND ADMINISTRATION

Therapy with TRADENAME should not exceed 12 weeks in duration.

Instructions for Use/Handling TRADENAME

Just prior to administration, remove the TRADENAME orally disintegrating tablet from the bottle with dry hands. Immediately place the tablet on top of the tongue, wait until it disintegrates, then swallow with saliva. The tablet typically disintegrates in about one and one half minutes. Administration with liquid is not necessary.

For the Relief of Symptomatic Gastroesophageal Reflux

Administer from 10 mg to 15 mg of TRADENAME orally up to four times daily, 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response (see **CLINICAL PHARMACOLOGY** and **INDICATIONS AND USAGE**). If symptoms occur only intermittently or at specific times of the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients

(such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

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

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

For the Relief of Symptoms Associated with Diabetic Gastroparesis (Diabetic Gastric Stasis)

Administer 10 mg of TRADENAME 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 TRADENAME 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, TRADENAME™ 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

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

Bottles of 100

NDC 0091-3331-01

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

NDA 21-793

Page 15

Bottles of 100

NDC 0091-3332-01

80-03301-

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

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

Manufactured for:

SCHWARZ
P H A R M A

MILWAUKEE, WI 53201, USA

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

TRADENAME uses CIMA® U.S. Patent Nos. 6,024,981 and 6,221,392.

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

PC4788
Rev. 03/04

80-03301-900

Trade Label 5 mg

NDC 0091-3331-01

100 tablets

TRADENAME™ 5 mg
(metoclopramide orally disintegrating tablets)

Rx only

SCHWARZ
P H A R M A

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Each orange-flavored, orally disintegrating tablet contains 5 mg metoclopramide base as the monohydrochloride monohydrate. Phenylethanolamine tartrate contains phenylethanolamine 4.2 mg per tablet.

USUAL DOSAGE: See package insert for further information. Store at 20° to 25° C (68° to 77° F); excursions permitted between 15° to 30° C (59° to 86° F) [See USP Controlled Room Temperature]. Protect from moisture.

Keep in a tight, light-resistant container as defined in the USP definition. **KEEP OUT OF REACH OF CHILDREN.**

Manufactured for:
SCHWARZ PHARMA, Inc.
Milwaukee, WI 53201, USA
By: CIMIA LABS INC.
Eden Prairie, MN 55244, USA
L4760
Rev. 02/04

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44-03097-900

LOT:
EXP:

Measurements

T 15.64 pt, .148" h

m 9.5 pt, .091" h

Trade Label 10 mg

<p>NDC 0091-3332-01</p>	<p>100 tablets</p>	<p>LOT: EXP:</p>
<p>Each orange-flavored, orally disintegrating tablet contains 10 mg metoprolamide base as the monohydrochloride monohydrate. Phenyleketonuric: contains phenylalanine 8.3 mg per tablet.</p> <p>USUAL DOSAGE: See package insert for further information. Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from moisture. Dispense in a tight, light-resistant container as defined in the USP/NF.</p> <p>KEEP OUT OF REACH OF CHILDREN.</p>		
<p>TRADENAME™ 10 mg (metoprolamide orally disintegrating tablets)</p> <p>Rx only</p>		
<p>SCHWARZ P H A R M A</p> <p>Manufactured for: SCHWARZ PHARMA, Inc. Milwaukee, WI 53201, USA By: CIMA LABS INC. Eden Prairie, MN 55244, USA L476 Rev. 02/04 44-0098-900</p>		

Measurements
T 15.88 pt, .151" h
m 9.6 pt, .092" h

Sample Display Carton 5 mg
Front and Side Panels

Measurements

T 17.47 pt, .166" h

m 8.935 pt, .097" h

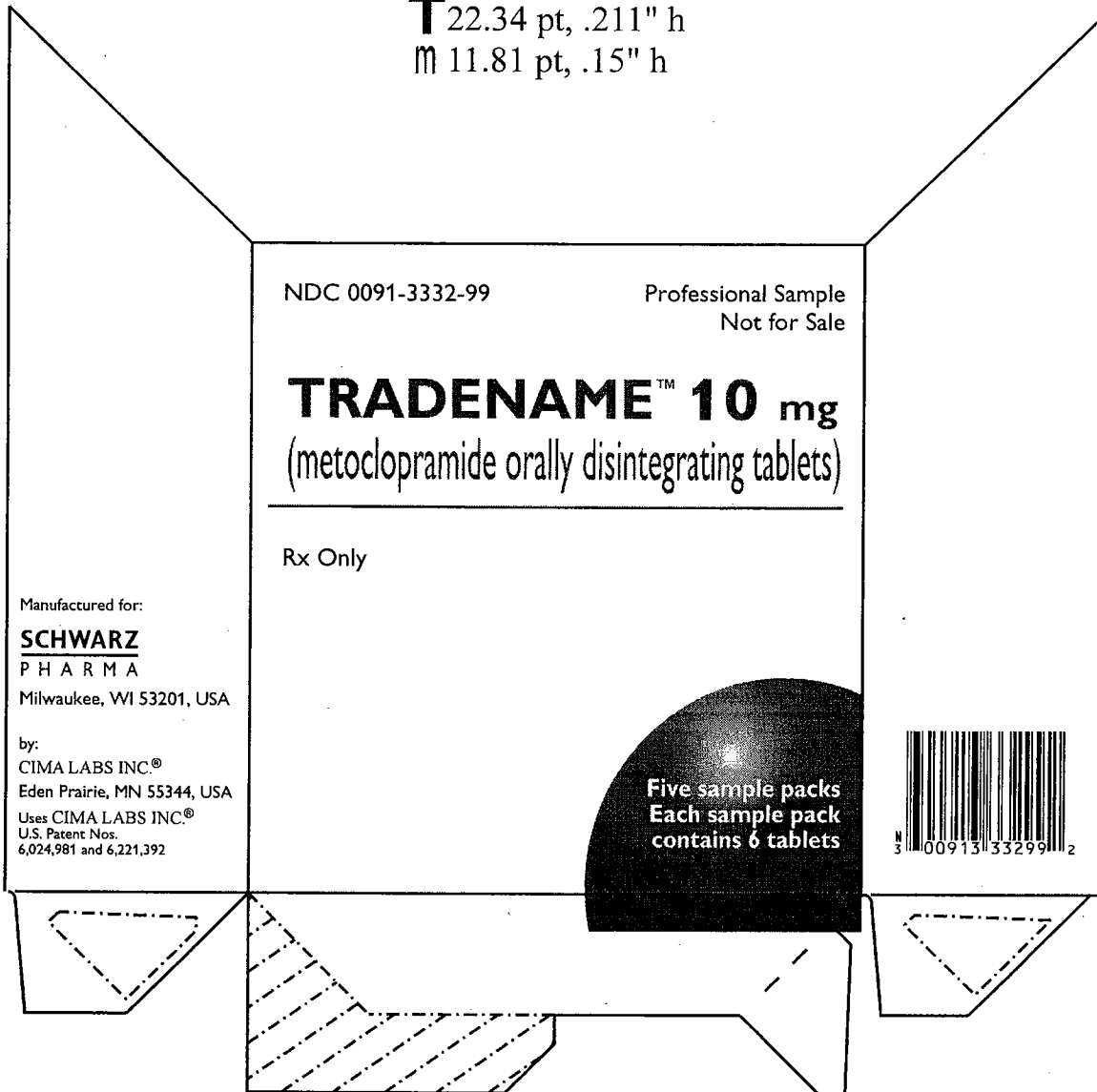


Sample Display Carton 10 mg
Front and Side Panels

Measurements

T 22.34 pt, .211" h

M 11.81 pt, .15" h



NDC 0091-3332-99

Professional Sample
Not for Sale

TRADENAME™ 10 mg
(metoclopramide orally disintegrating tablets)

Rx Only

Manufactured for:

SCHWARZ
P H A R M A

Milwaukee, WI 53201, USA

by:

CIMA LABS INC.®

Eden Prairie, MN 55344, USA

Uses CIMA LABS INC.®

U.S. Patent Nos.
6,024,981 and 6,221,392

Five sample packs
Each sample pack
contains 6 tablets



Sample Blister Card 5 mg

Measurements

$T = 9.0 \text{ pt}, .086" \text{ h}$
 $m = 6.0 \text{ pt}, .05" \text{ h}$

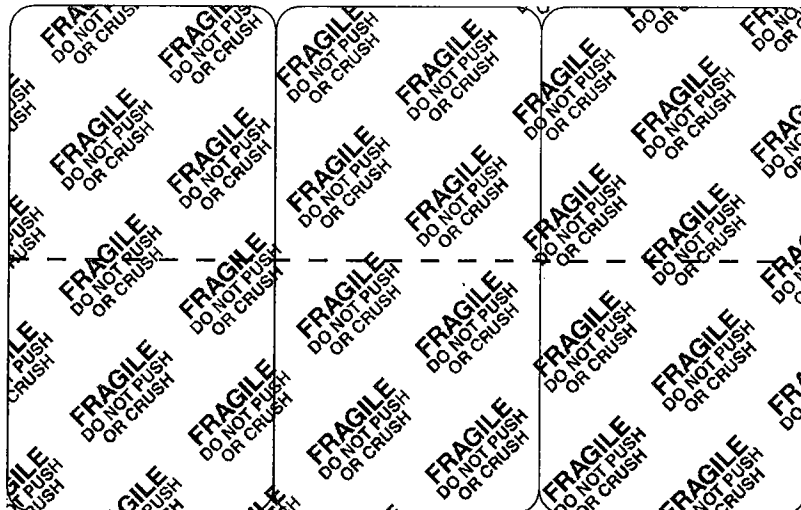
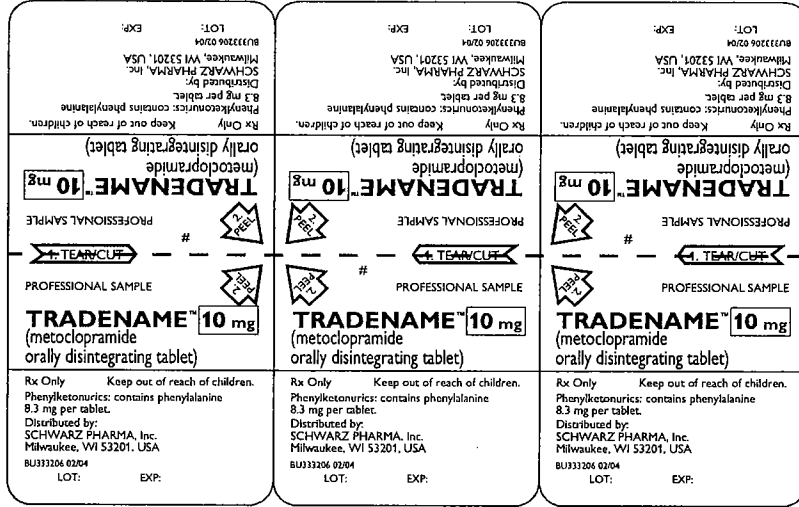
LOT: BU33106 02/04 EXP:	LOT: BU33106 02/04 EXP:	LOT: BU33106 02/04 EXP:
Distributed by: SCHWARZ PHARMA, Inc. Milwaukee, WI 53201, USA 4.2 mg per tablet Phenyletonics: contains phenylalanine Rx Only Keep out of reach of children.	Distributed by: SCHWARZ PHARMA, Inc. Milwaukee, WI 53201, USA 4.2 mg per tablet Phenyletonics: contains phenylalanine Rx Only Keep out of reach of children.	Distributed by: SCHWARZ PHARMA, Inc. Milwaukee, WI 53201, USA 4.2 mg per tablet Phenyletonics: contains phenylalanine Rx Only Keep out of reach of children.
PROFESSIONAL SAMPLE # TEAR/CUT	PROFESSIONAL SAMPLE # TEAR/CUT	PROFESSIONAL SAMPLE # TEAR/CUT
TRADENAME™ 5 mg (metoclopramide orally disintegrating tablet)	TRADENAME™ 5 mg (metoclopramide orally disintegrating tablet)	TRADENAME™ 5 mg (metoclopramide orally disintegrating tablet)
Rx Only Keep out of reach of children. Phenyletonics: contains phenylalanine 4.2 mg per tablet. Distributed by: SCHWARZ PHARMA, Inc. Milwaukee, WI 53201, USA BU33106 02/04 LOT: EXP:	Rx Only Keep out of reach of children. Phenyletonics: contains phenylalanine 4.2 mg per tablet. Distributed by: SCHWARZ PHARMA, Inc. Milwaukee, WI 53201, USA BU33106 02/04 LOT: EXP:	Rx Only Keep out of reach of children. Phenyletonics: contains phenylalanine 4.2 mg per tablet. Distributed by: SCHWARZ PHARMA, Inc. Milwaukee, WI 53201, USA BU33106 02/04 LOT: EXP:

FRAGILE DO NOT PUSH OR CRUSH	FRAGILE DO NOT PUSH OR CRUSH	FRAGILE DO NOT PUSH OR CRUSH
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FRAGILE DO NOT PUSH OR CRUSH	FRAGILE DO NOT PUSH OR CRUSH	FRAGILE DO NOT PUSH OR CRUSH

Sample Blister Card 10 mg

Measurements

T 9.0 pt, .086" h
m 6.0 pt, .05" h



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

/s/

Joyce Korvick
6/10/05 02:08:50 PM