

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REGLAN ODT™ safely and effectively. See full prescribing information for REGLAN ODT™.

REGLAN ODT™ (metoclopramide) orally disintegrating tablets
Initial U.S. Approval: 1979

WARNING: TARDIVE DYSKINESIA

See full prescribing information for complete boxed warning.

Treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible.

Metoclopramide therapy should be discontinued in patients who develop signs or symptoms of tardive dyskinesia.

Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing tardive dyskinesia. (5.1)

INDICATIONS AND USAGE

REGLAN ODT™ is a dopamine receptor antagonist indicated for:

- **Symptomatic Gastroesophageal Reflux:** Short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy. (1.1)
- **Diabetic Gastroparesis (Diabetic Gastric Stasis):** The relief of symptoms associated with acute and recurrent diabetic gastric stasis. (1.2)
- **Important Limitations**
The use of REGLAN ODT™ is recommended for adults only. Safety and effectiveness in pediatric patients have not been established. (8.4)
- Therapy should not exceed 12 weeks in duration (1.3)

DOSAGE AND ADMINISTRATION

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

- **Symptomatic Gastroesophageal Reflux:** 10 mg to 15 mg orally up to four times daily, 30 minutes before each meal and at bedtime. (2.2)
- **Diabetic Gastroparesis (Diabetic Gastric Stasis):** 10 mg 30 minutes before each meal and at bedtime for two to eight weeks. (2.3)
- **Patients with Renal Impairment:** In patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. (2.4)
- REGLAN ODT™ can be taken without liquid (2.1)

DOSAGE FORMS AND STRENGTHS

- Orally Disintegrating Tablets: 5mg and 10mg (3)

CONTRAINDICATIONS

- Gastrointestinal hemorrhage, mechanical obstruction, or perforation (4.1)
- Pheochromocytoma (4.2)

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ADVERSE REACTIONS

The most common adverse reactions (approx. 10%) are CNS effects such as, restlessness, drowsiness, fatigue and lassitude. Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation occur less frequently.

To report SUSPECTED ADVERSE REACTIONS, contact Alaven Pharmaceutical LLC at 1-888-317-0001 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Anticholinergic drugs:** Antagonize the effects of metoclopramide (7.1)
- **Narcotic analgesic drugs:** May increase sedation (7.1)
- **Monoamine oxidase inhibitors:** May cause hypertensive crisis due to catecholamine release (7.2)
- **Altered drug absorption:** May decrease absorption of drugs from the stomach (e.g. digoxin) and increase absorption of drugs from the small bowel (7.3)
- **Insulin:** Adjustment of insulin dose or timing may be required to avoid hypoglycemia (7.4)

USE IN SPECIFIC POPULATIONS

- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. (8.4)
- **Geriatric Use:** Elderly patients may be more sensitive to adverse reactions such as sedation and drug-induced movement disorders. (8.5)
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Revised: 09/2010

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WARNING: TARDIVE DYSKINESIA

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

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

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

[See Warnings and Precautions (5.1)]

1 INDICATIONS AND USAGE

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

1.1 Symptomatic Gastroesophageal Reflux

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

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

1.2 Diabetic Gastroparesis (Diabetic Gastric Stasis)

REGLAN ODT™ is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) appear to respond to metoclopramide within different time intervals.

1.3 Important Limitations

REGLAN ODT™ is indicated for adults only. Therapy should not exceed 12 weeks in duration. The safety and effectiveness in pediatric patients have not been established.

2 DOSAGE AND ADMINISTRATION

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

2.1 Instructions for Use/Handling REGLAN ODT™

Just prior to administration, remove the REGLAN ODT™ orally disintegrating tablet from the packaging with dry hands. The tablet should be removed from the package 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.

2.2 Symptomatic Gastroesophageal Reflux Disease

For the relief of symptomatic, documented gastroesophageal reflux disease (GERD), therapy should not exceed 12 weeks.

Administer from 10 mg to 15 mg of REGLAN ODT™ orally up to four times daily, 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response [see *Clinical Pharmacology (12.1)* and *Indications and Usage (1.1)*]. 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 (6)*]. Because of the poor correlation between symptoms and endoscopic appearance of the esophagus, therapy directed at esophageal lesions is best guided by endoscopic evaluation.

Prolonged treatment (>12 weeks) with metoclopramide should be avoided in all but rare cases where therapeutic benefit is thought to counterbalance the risks to the patient of developing tardive dyskinesia. [see *Warnings and Precautions (5.1)*].

2.3 Diabetic Gastroparesis (Diabetic Gastric Stasis)

For the relief of symptoms associated with diabetic gastroparesis (diabetic gastric stasis), therapy of two to eight weeks is recommended. Therapy should not exceed 12 weeks in duration.

Administer 10 mg of REGLAN ODT™ 30 minutes before each meal and at bedtime for two to eight weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation.

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

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

2.4 Patients with Renal 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 *Use in Specific Populations (8.7) and Overdosage (10)*]

3 DOSAGE FORMS AND STRENGTHS

REGLAN ODT™ (metoclopramide) orally disintegrating tablets contains either 5 mg or 10 mg of metoclopramide base (as monohydrochloride monohydrate). The tablets are white, round, flat-faced, and orange flavored.

4 CONTRAINDICATIONS

4.1 Gastrointestinal Hemorrhage, Mechanical Obstruction, or Perforation

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).

4.2 Pheochromocytoma

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.

4.3 Known Sensitivity or Intolerance

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

4.4 Epilepsy

Metoclopramide should not be used in epileptics since the frequency and severity of seizures may be increased.

4.5 Concomitant Medications with Extrapyramidal Reactions

Metoclopramide should not be used in patients receiving other drugs that are likely to cause extrapyramidal reactions, since the frequency and severity of extrapyramidal reactions may be increased. [See *Warnings and Precautions (5.2), Adverse Reactions (6), and Drug Interactions (7.5)*]

5 WARNINGS AND PRECAUTIONS

5.1 Tardive Dyskinesia (see Boxed Warnings)

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

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

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

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

5.2 Acute Dystonic Reactions, Drug-induced Parkinsonism, and Other Extrapyramidal Symptoms

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. 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.

5.3 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 (6.3)*].

5.4 Depression

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.

5.5 Hypertension

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. There are also clinical reports of hypertensive crises in some patients with undiagnosed pheochromocytoma, thus any rapid rise in blood pressure associated with REGLAN ODT use should result in immediate cessation of metoclopramide use in those patients [*see Contraindications (4.2)*].

5.6 Congestive Heart Failure and Ventricular Arrhythmia

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.

5.7 Withdrawal from Metoclopramide

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

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In the listing below, the incidence of adverse reactions correlates with the dose and duration of metoclopramide administration as reported in the medical literature around the time of metoclopramide's initial approval. In most instances, the reported adverse reactions data do not permit an estimate of

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

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. Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation [see *Warnings and Precautions (5)*] occur less frequently. The incidence of drowsiness is greater at higher doses. There are isolated reports of convulsive seizures without clear-cut relationship to metoclopramide. Rarely, hallucinations have been reported.

Extrapyramidal Reactions (EPS)

Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (tetanus-like reactions), and, rarely, stridor and dyspnea possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine [see *Warnings and Precautions (5)*].

Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies [see *Warnings and Precautions (5)*].

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 and Precautions (5.1)*].

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 and Precautions (5.2)*].

Endocrine Disturbances

Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia Fluid retention secondary to transient elevation of aldosterone [see *Clinical Pharmacology (12.1)*].

Cardiovascular

Hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention, acute congestive heart failure and possible AV block [see *Contraindications (4) and Warnings and Precautions (5.3)*].

Gastrointestinal

Nausea and bowel disturbances, primarily diarrhea.

Hepatic

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

Renal

Urinary frequency and incontinence.

Hematologic

A few cases of neutropenia, leukopenia, or agranulocytosis, generally without clear-cut relationship to metoclopramide. Methemoglobinemia, in adults and especially with overdosage in neonates [see *Overdosage (10)*]. 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.

7

DRUG INTERACTIONS

The effects of metoclopramide on gastrointestinal motility can impact the absorption of other drugs. The known drug-drug interactions are listed below.

7.1 Anticholinergic and narcotic analgesic drugs

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.

7.2 Monoamine oxidase inhibitors

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.

7.3 Altered Drug Absorption

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).

7.4 Insulin

Insulin dosage or timing of dosage may require adjustment because the action of metoclopramide will hasten the movement of food to the intestines and therefore the rate of absorption. Increasing movement of food to the intestines may lead to absorption of less glucose from a meal, hence less glucose in the circulation for a particular dose of administered insulin to act upon, resulting in hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 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.

8.2 Labor and Delivery

The use of metoclopramide in labor and delivery has not been studied.

8.3 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.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established [see *Overdosage (10)*].

Care should be exercised in administering metoclopramide to neonates since prolonged clearance may produce excessive serum concentrations [see *Clinical Pharmacology (12.3)*]. 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, a possible side effect of metoclopramide use in neonates [see *Overdosage (10)*].

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 Precautions (5)* and *Adverse Reactions (6.2)*]

8.5 Geriatric Use

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

The risk of developing parkinsonian-like side effects increases with ascending dose. Geriatric patients should receive the lowest dose of REGLAN ODT™ that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving REGLAN ODT™, REGLAN ODT™ should be discontinued before initiating any specific anti-parkinsonian agents [see *Warnings and Precautions (5)* and *Dosage and Administration (2)*].

The elderly may be at greater risk for tardive dyskinesia [see *Warnings and Precautions (5.1)*].

Sedation has been reported in metoclopramide users. Sedation may cause confusion and manifest as over-sedation in the elderly [see *Clinical Pharmacology (12.1)*, *Adverse Reactions (6.1)*, and *Patient Counseling Information (17.1)*].

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 (2.4)*].

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 (2)*].

8.6 Hepatic Insufficiency

Metoclopramide has been safely used in patients with advanced liver disease whose renal function was normal.

8.7 Renal Insufficiency

Renally impaired patients whose creatinine clearance is below 40 mL/min may be more sensitive to the therapeutic dose or the adverse effects of metoclopramide. Therefore, these patients should start therapy at a lower dose (approximately half the recommended dosage) and the dose should be titrated according to their overall clinical response and/or adverse event profile. Dialysis is not likely to be an effective method of drug removal in overdose situations. (See *Dosage and Administration (2.4)*)

8.8 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 (10)*].

10 OVERDOSAGE

Symptoms of overdose 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 may 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.

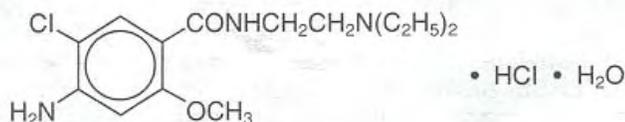
Unintentional overdose due to misadministration has been reported in infants and children with the use of metoclopramide oral solution. While there was no consistent pattern to the reports associated with these overdoses, events included seizures, extrapyramidal reactions, and lethargy.

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 *Use in Specific Populations (8.6)*].

11 DESCRIPTION

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

Metoclopramide hydrochloride is a white crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its molecular formula is C₁₄H₂₂ClN₃O₂•HCl•H₂O. 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

The antiemetic properties of metoclopramide appear to be primarily 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 and Precautions (5)*]. 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.

12.2 Pharmacodynamics

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.

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.

12.3 Pharmacokinetics

Absorption:

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

In a single dose study of 12 subjects, the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same. Linear kinetic processes adequately describe the absorption of metoclopramide.

Distribution:

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.

Excretion:

In a single dose study of 12 subjects with doses from 20 to 100 mg, whole body clearance is unchanged; and the elimination rate remains the same. The mean elimination half-life of metoclopramide is approximately 7 hr after administration of REGLAN ODT™. Linear kinetic processes adequately describe the 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.

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

Special Populations

Renal Insufficiency:

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.

Pediatric Patients:

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

A 77-week study was conducted in rats with oral doses of metoclopramide up to 40 mg/kg/day (about 5 times the maximum recommended human dose on surface area basis). Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

REGLAN ODT™ (metoclopramide) orally disintegrating tablets 5 mg base (as the monohydrochloride monohydrate) are white, round, flat-faced, orange-flavored and engraved “AP” on one side and “152” on the other side. They are supplied as follows:

Bottles of 100 NDC 68220-152-10

REGLAN ODT™ (metoclopramide) orally disintegrating tablets 10 mg base (as the monohydrochloride monohydrate) are white, round, flat-faced, orange-flavored and engraved “AP” on one side and “153” on the other side. They are supplied as follows:

Bottles of 100 NDC 68220-153-10

16.2 Storage and Handling

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.

17 PATIENT COUNSELING INFORMATION

[See Medication Guide]

Instruct patients to take REGLAN ODT at least 30 minutes before eating and at bedtime.

Instruct patients not to remove REGLAN ODT™ orally disintegrating tablets from the packaging until just prior to dosing. With dry hands, the patient should remove the tablet from the package and immediately place the tablet 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.

Inform patients or their caregivers of serious potential issues associated with metoclopramide use such as tardive dyskinesia, extrapyramidal symptoms, and neuroleptic malignant syndrome. Advise patients to inform their physician if symptoms associated with these disorders occur during or after treatment with REGLAN ODT.

Inform patients that metoclopramide may cause drowsiness, dizziness, or otherwise impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. Sedation may be more pronounced in the elderly. The ambulatory patient should be cautioned accordingly.

Inform patients that the most common adverse reactions in patients treated with REGLAN ODT or other metoclopramide-containing products are headache, nausea, vomiting, tiredness, sleepiness, dizziness, and restlessness.

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

For additional information, patients should be instructed to see the Medication Guide for REGLAN ODT™ printed at the end of the prescribing information.

Manufactured for:

ALAVEN[®]
PHARMACEUTICAL, LLC

Marietta, GA 30062

www.alavenpharm.com

For Medical Inquiries, call toll-free 1-888-317-0001.

Manufactured by:

CIMA[®] LABS INC.

Eden Prairie, MN 55344

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

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Medication Guide

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

Read the Medication Guide that comes with REGLAN ODT before you start taking it and each time you get a refill. There may be new information. If you take another product that contains metoclopramide (such as REGLAN tablets, REGLAN injection, or metoclopramide oral syrup), you should read the Medication Guide that comes with that product. Some of the information may be different. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about REGLAN ODT?

REGLAN ODT can cause serious side effects, including:

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

Your chances for getting TD go up:

- the longer you take REGLAN ODT and the more REGLAN ODT you take. You should not take REGLAN ODT for more than 12 weeks.
- if you are older, especially if you are a woman
- if you have diabetes.

It is not possible for your doctor to know if you will get TD if you take REGLAN ODT.

Call your doctor right away if you get movements you can not stop or control, such as:

- lip smacking, chewing, or puckering up your mouth
- frowning or scowling
- sticking out your tongue
- blinking and moving your eyes
- shaking of your arms and legs

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

What is REGLAN ODT?

REGLAN ODT is a prescription medicine used:

- in adults for 4 to 12 weeks to relieve heartburn symptoms with gastroesophageal reflux disease (GERD) when certain other treatments do not work. REGLAN ODT relieves daytime heartburn and heartburn after meals. It also helps ulcers in the esophagus to heal.

- to relieve symptoms of slow stomach emptying in people with diabetes. REGLAN ODT helps treat symptoms such as nausea, vomiting, heartburn, feeling full long after a meal, and loss of appetite. Not all these symptoms get better at the same time.

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

Who should not take REGLAN ODT?

Do not take REGLAN ODT if you:

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

What should I tell my doctor before taking REGLAN ODT?

Tell your doctor about all your medical conditions, including if you have:

- depression
- Parkinson's disease
- high blood pressure
- kidney problems. Your doctor may start with a lower dose.
- liver problems or heart failure. REGLAN ODT may cause your body to hold fluids.
- diabetes. Your dose of insulin may need to be changed.
- breast cancer
- phenylketonuria. REGLAN ODT contains aspartame.
- you are pregnant or plan to become pregnant. It is not known if REGLAN ODT will harm your unborn baby.
- you are breast-feeding. REGLAN ODT can pass into breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you take REGLAN ODT.

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

Especially tell your doctor if you take:

- another medicine that contains metoclopramide, such as REGLAN tablets, or metoclopramide oral syrup.
- a blood pressure medicine
- a medicine for depression, especially an Monoamine Oxidase Inhibitor (MAOI)
- insulin

- a medicine that can make you sleepy, such as an anti-anxiety medicine, sleep medicines, and narcotics.

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

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

How should I take REGLAN ODT?

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

What should I avoid while taking REGLAN ODT?

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

What are the possible side effects of REGLAN ODT?

Reglan ODT can cause serious side effects, including:

- **Abnormal muscle movements.** See “What is the most important information I should know about REGLAN ODT?”
- **Uncontrolled spasm of your face and neck muscles, or muscles of your body, arms, and legs (dystonia).** These muscle spasms can cause abnormal movements and body positions. These spasms usually start within the first 2 days of treatment. These spasms happen more often in children and adults under age 30.
- **Depression, thoughts about suicide, and suicide.** Some people who take REGLAN ODT become depressed. You may have thoughts about hurting or killing yourself. Some people who take REGLAN ODT have ended their own lives (suicide).

- **Neuroleptic Malignant Syndrome (NMS).** NMS is a rare but very serious condition that can happen with REGLAN ODT. NMS can cause death and must be treated in a hospital. Symptoms of NMS include: high fever, stiff muscles, problems thinking, very fast or uneven heartbeat, and increased sweating.
- **Parkinsonism.** Symptoms include slight shaking, body stiffness, trouble moving or keeping your balance. If you already have Parkinson's disease, your symptoms may become worse while you are receiving REGLAN ODT.

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

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

Common side effects include:

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

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

You may still have side effects after you stop REGLAN ODT. You may have symptoms from stopping (withdrawal) REGLAN ODT such as headaches, and feeling dizzy or nervous.

Tell your doctor about any side effects that bother you or do not go away. These are not all the possible side effects of REGLAN ODT.

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

How do I store REGLAN ODT?

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

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

General information about REGLAN ODT

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

This Medication Guide summarizes the most important information about REGLAN ODT. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about REGLAN ODT that is written for health professionals. For more information go to www.alavenpharma.com or call 1-888-317-0001.

What are the ingredients in REGLAN ODT?

Active ingredient: metoclopramide

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

Manufactured for

Alaven Pharmaceutical LLC, Marietta, GA 30062

Revised June 2009

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