REGLAN Injection (metoclopramide injection, USP)

R_x only

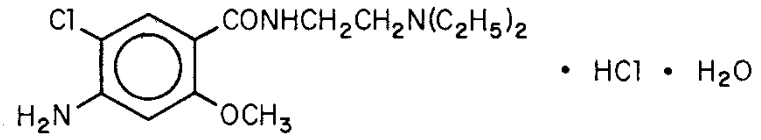
WARNING: TARDIVE DYSKINESIA

- **Metoclopramide, including REGLAN Injection, can cause tardive dyskinesia (TD), a potentially irreversible serious movement disorder. In patients treated with metoclopramide, including REGLAN Injection, the risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dosage.**
- **REGLAN Injection is contraindicated in patients with a history of TD.**
- **Immediately discontinue REGLAN Injection in patients who develop signs or symptoms of TD.**
- **In patients with diabetic gastroparesis, avoid a total duration of treatment with metoclopramide products, including REGLAN Injection, for longer than 12 weeks. If longer-term use is unavoidable, routinely monitor for signs and symptoms of TD.**

See WARNINGS.

DESCRIPTION

Metoclopramide hydrochloride is a white crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Molecular weight: 354.3.



$C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$

REGLAN Injection (metoclopramide injection, USP) is a clear, colorless, sterile solution with a pH of 4.5-6.5 for intravenous (IV) or intramuscular (IM) administration.

This product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

2 mL single dose vials; 10 mL and 30 mL single dose vials

Each 1 mL contains: Metoclopramide base 5 mg (as the monohydrochloride monohydrate), Sodium Chloride, USP 8.5 mg, Water for Injection, USP q.s. pH adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide.

CLINICAL PHARMACOLOGY

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

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

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

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

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

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

Pharmacokinetics

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

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 5-6 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 (see Table 1).

Table 1. Adult Pharmacokinetic Data

Parameter	Value
Vd (L/kg)	~ 3.5
Plasma Protein Binding	~ 30%
$t_{1/2}$ (hr)	5-6
Oral Bioavailability	80%±15.5%

Patients with Renal Impairment

In a study of 24 patients with varying degrees of renal impairment (moderate, severe, and end-stage renal disease (ESRD) requiring dialysis), the systemic exposure (AUC) of metoclopramide following intravenous administration in patients with moderate to severe renal impairment was about 2-fold the AUC in subjects with normal renal function. The AUC of metoclopramide in patients with ESRD in dialysis was about 3.5-fold the AUC in subjects with normal renal function.

Patients with Hepatic Impairment

In a group of 8 patients with severe hepatic impairment (Child-Pugh C) administered intravenous metoclopramide, the average metoclopramide clearance was reduced by approximately 50% compared to patients with normal hepatic function.

Effect of CYP2D6 Inhibitors on Metoclopramide

In healthy subjects, 20 mg of oral metoclopramide and 60 mg of fluoxetine (a strong CYP2D6 inhibitor) were administered, following prior exposure to 60 mg fluoxetine orally for 8 days. The patients who received concomitant metoclopramide and fluoxetine had a 40% and 90% increase in metoclopramide C_{max} and $AUC_{0-\infty}$, respectively, compared to patients who received metoclopramide alone (see Table 2).

Table 2. Oral Metoclopramide Pharmacokinetic Parameters in Healthy Subjects with and without Fluoxetine

Parameter	Metoclopramide alone (mean ±SD)	Metoclopramide with fluoxetine (mean ±SD)
C_{max} (ng/mL)	44±15	62.7±9.2
$AUC_{0-\infty}$ (ng·h/mL)	313±113	591±140
$T_{1/2}$(h)	5.5±1.1	8.5±2.2

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.

INDICATIONS AND USAGE

Diabetic Gastroparesis

REGLAN Injection (metoclopramide hydrochloride, USP) is indicated for the relief of symptoms associated with acute and recurrent diabetic gastroparesis is in adults.

The Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy

REGLAN Injection is indicated for the prophylaxis of vomiting associated with emetogenic cancer chemotherapy in adults.

The Prevention of Postoperative Nausea and Vomiting

REGLAN Injection is indicated for the prophylaxis of postoperative nausea and vomiting in those circumstances where nasogastric suction is undesirable in adults.

Small Bowel Intubation

REGLAN Injection is indicated to facilitate small bowel intubation in adult and pediatric patients in whom the tube does not pass the pylorus with conventional maneuvers.

Radiological Examination

REGLAN Injection is indicated to stimulate gastric emptying and intestinal transit of barium where delayed emptying interferes with radiological examination of the stomach and/or small intestine in adults.

CONTRAINDICATIONS

REGLAN Injection is contraindicated:

- in patients with a history of tardive dyskinesia (TD) or a dystonic reaction to metoclopramide. See **WARNINGS**.
- whenever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.
- in patients with pheochromocytoma or other catecholamine-releasing paragangliomas. Metoclopramide may cause a hypertensive/pheochromocytoma crisis, probably due to release of catecholamines from the tumor.
- in patients with known sensitivity or intolerance to metoclopramide.
- in patients with epilepsy. REGLAN Injection may increase the frequency and severity of seizures.

WARNINGS

Tardive Dyskinesia (see BOXED WARNING)

Metoclopramide, including REGLAN Injection, can cause tardive dyskinesia (TD), a syndrome of potentially irreversible and disfiguring involuntary movements of the face or tongue, and sometimes of the trunk and/or extremities. Metoclopramide, including REGLAN Injection, may also suppress, or partially suppress, the signs of TD, and may delay the diagnosis of TD because it may mask the underlying disease process. The effect of the symptomatic suppression upon the

long-term course of TD is unknown. TD may remit, partially or completely, if treatment with REGLAN Injection is discontinued.

In patients treated with metoclopramide, including REGLAN Injection, the risk of developing TD and the likelihood that TD will become irreversible increases with duration of treatment and total cumulative dosage. Additionally, the risk of developing TD is increased in elderly patients, especially in elderly women, and in patients with diabetes mellitus.

Prevention, Mitigation, and Monitoring for TD

- REGLAN Injection, contraindicated in patients with history of TD
- Avoid use of REGLAN Injection in patients receiving concomitant antipsychotics due to the potential additive effects of TD.
- Reduce the dosage of REGLAN Injection in the elderly. (see **DOSAGE AND ADMINISTRATION, Renal and Hepatic Impairment**).
- Immediately discontinue REGLAN Injection immediately in patients who develop signs and symptoms of TD.
- In patients with diabetic gastroparesis, avoid a total duration of treatment with metoclopramide products, including REGLAN Injection, for longer than 12 weeks. If longer-term use is unavoidable, routinely monitor for signs and symptoms of TD.
- If patients have continued TD symptoms, consider TD treatment.

Other Extrapyramidal Symptoms

In addition to TD, metoclopramide may cause other extrapyramidal symptoms (EPS), parkinsonian symptoms, and motor restlessness. Advise patients to seek immediate medical attention if such symptoms occur and to discontinue REGLAN Injection.

- Extrapyramidal symptoms (EPS), such as acute dystonic reactions, occurred in patients treated with metoclopramide dosages of 30 mg to 40 mg daily. Such reactions occurred more frequently in adults less than 30 years of age and at the higher dosages used in prophylaxis of vomiting due to cancer chemotherapy. EPS occurred more frequently in pediatric patients compared to adults (REGLAN Injection is only approved in pediatric patients for small bowel intubation). Symptoms can occur in the first 24 to 48 hours after starting metoclopramide. Symptoms included 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 were present as stridor and dyspnea, possibly due to laryngospasm. Diphenhydramine hydrochloride or benztropine mesylate may be used to treat these adverse reactions. Avoid REGLAN Injection in patients receiving other drugs that can cause EPS (e.g., antipsychotics).
- Parkinsonian symptoms (bradykinesia, tremor, cogwheel rigidity, mask-like facies), have occurred after starting metoclopramide, more commonly within the first 6 months, but also after longer periods. Symptoms generally have subsided within 2 to 3 months after discontinuation of metoclopramide. Avoid REGLAN injection in patients with Parkinson's disease and other patients being treated with antiparkinsonian drugs due to potential exacerbation of symptoms. If treatment is unavoidable, use REGLAN Injection

for the shortest duration of treatment and periodically reassess the need for continued treatment. Routinely monitor for signs and symptoms of Parkinson's disease.

- Motor restlessness (akathisia) has developed and consisted of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing, and foot tapping. If symptoms resolve, consider restarting at a lower dosage.

Neuroleptic Malignant Syndrome

Metoclopramide may cause a potentially fatal symptom complex called neuroleptic malignant syndrome (NMS). NMS has been reported in association with metoclopramide overdosage and concomitant treatment with another drug associated with NMS. Avoid REGLAN Injection in patients receiving other drugs associated with NMS, including typical and atypical antipsychotics.

Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and manifestations of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac arrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Patients with such symptoms should be evaluated immediately.

In the diagnostic evaluation, consider the presence of other serious medical conditions (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, malignant hyperthermia, drug fever, serotonin syndrome, and primary central nervous system pathology.

Management of NMS includes:

- Immediate discontinuation of REGLAN Injection and other drugs not essential to concurrent therapy (see **PRECAUTIONS – Drug Interactions**).
- Intensive symptomatic treatment and medical monitoring.
- Treatment of any concomitant serious medical problems for which specific treatments are available

Depression

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.

PRECAUTIONS

Hypertension

In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; avoid REGLAN Injection in patients with hypertension or patients taking monoamine oxidase inhibitors (see **PRECAUTIONS – Drug Interactions**).

There are also clinical reports of hypertensive crises in patients with undiagnosed pheochromocytoma. REGLAN Injection is contraindicated in patients with pheochromocytoma or other catecholamine-releasing paragangliomas. Discontinue REGLAN Injection in any patient with a rapid rise in blood pressure.

Fluid Overload
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. Discontinue REGLAN Injection if any of these adverse reactions occur.

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

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

Anastamotic Dehiscence
Giving a promotility drug such as metoclopramide theoretically could put increased pressure on suture lines following a gut anastomosis or closure. This possibility should be considered and weighed when deciding whether to use REGLAN Injection or nasogastric suction in the prevention of postoperative nausea and vomiting.

Effects on the Ability to Drive and Operate Machinery
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. Concomitant use of central nervous system (CNS) depressants or drugs associated with EPS may increase this effect (e.g., alcohol, sedatives, hypnotics, opiates, and anxiolytics). Avoid REGLAN Injection or the interacting drug, depending on the importance of the drug to the patient.

Drug Interactions
Effects of Other Drugs on Metoclopramide

Table 3 displays the effects of other drugs on metoclopramide.

Table 3. Effects of Other Drugs on Metoclopramide

Antipsychotics	
Clinical Impact	Potential for additive effects, including increased frequency and severity of tardive dyskinesia (TD), other extrapyramidal symptoms (EPS), and neuroleptic malignant syndrome (NMS).
Intervention	Avoid concomitant use.
Strong CYP2D6 Inhibitors, not Included in Antipsychotic Category Above	
Clinical Impact	Increased plasma concentrations of metoclopramide; risk of exacerbation of extrapyramidal symptoms.
Intervention	Avoid REGLAN Injection. If use is unavoidable, monitor for adverse reactions
Examples	quinidine, bupropion, fluoxetine, and paroxetine
Monoamine Oxidase Inhibitors	
Clinical Impact	Increased risk of hypertension.
Intervention	Avoid concomitant use.
Central Nervous System (CNS) Depressants	
Clinical Impact	Increased risk of CNS depression.
Intervention	Avoid REGLAN Injection or the interacting drug, depending on the importance of the drug to the patient
Examples	alcohol, sedatives, hypnotics, opiates and anxiolytics
Drugs that Impair Gastrointestinal Motility	
Clinical Impact	Decreased systemic absorption of metoclopramide.
Intervention	Monitor for reduced therapeutic effect.

Examples	antiperistaltic antidiarrheal drugs, anticholinergic drugs, and opiates
Dopaminergic Agonists and Other Drugs that Increase Dopamine Concentrations	
Clinical Impact	Decreased therapeutic effect of metoclopramide due to opposing effects on dopamine.
Intervention	Monitor for reduced therapeutic effect.
Examples	apomorphine, bromocriptine, cabergoline, levodopa, pramipexole, ropinirole, and rotigotine

Effects of Metoclopramide on Other Drugs

Table 4 displays the effects of metoclopramide on other drugs.

Table 4. Effects of Metoclopramide on Other Drugs

Dopaminergic Agonists and Drugs Increasing Dopamine Concentrations	
Clinical Impact	Opposing effects of metoclopramide and the interacting drug on dopamine. Potential exacerbation of symptoms (e.g., parkinsonian symptoms).
Intervention	Avoid concomitant use.
Examples	Apomorphine, bromocriptine, cabergoline, levodopa, pramipexole, ropinirole, rotigotine
Succinylcholine, Mivacurium	
Clinical Impact	Metoclopramide inhibits plasma cholinesterase leading to enhanced neuromuscular blockade.
Intervention	Monitor for signs and symptoms of prolonged neuromuscular blockade
Drugs with Absorption Altered due to Increased Gastrointestinal Motility	
Clinical Impact	The effect of metoclopramide on other drugs is variable. Increased gastrointestinal (GI) motility by metoclopramide may impact absorption of other drugs leading to decreased or increased drug exposure.
Intervention	Drugs with Decreased Absorption (e.g., digoxin, atovaquone, posaconazole oral suspension*, fosfomycin): Monitor for reduced therapeutic effect of the interacting drug. For digoxin monitor therapeutic drug concentrations and increase the digoxin dose as needed (see prescribing information for digoxin). Drugs with Increased Absorption (e.g., sirolimus, tacrolimus, cyclosporine): Monitor therapeutic drug concentrations and adjust the dose as needed. See prescribing information for the interacting drug.
Insulin	
Clinical Impact	Increased GI motility by metoclopramide may increase delivery of food to the intestines and increase blood glucose.
Intervention	Monitor blood glucose and adjust insulin dosage regimen as needed.

*Interaction does not apply to posaconazole delayed-release tablets

Information for Patients

A patient Medication Guide is available for REGLAN Injection. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. Refer to accompanying Medication Guide.

Tardive Dyskinesia and/or other Extrapyramidal Reactions

REGLAN injection may cause tardive dyskinesia or other extrapyramidal symptoms, parkinsonian symptoms, and motor restlessness. Instruct patients to immediately contact their healthcare provider if symptoms occur. See **WARNINGS**.

Neuroleptic Malignant Syndrome

Serious neuroleptic malignant syndrome (NMS) has been reported in association with concomitant treatment of metoclopramide with another drug associated with NMS. Advise patients to report all prescription and over-the-counter medications to the healthcare provider. Instruct patients to seek medical attention if symptoms occur.

Depression and/or Possible Suicidal Ideation

Symptoms of new onset or worsening depression as well as suicidal ideation have been reported in patients taking metoclopramide. Instruct patients to contact their healthcare provider if any of these symptoms occur.

Drug Interactions

Concomitant treatment with numerous other medications can precipitate or worsen serious adverse reactions such as tardive dyskinesia or other extrapyramidal reactions, neuroleptic malignant syndrome, and CNS depression. Advise patients to report all prescriptions and over the counter medications to the healthcare provider.

Effects on the Ability to Drive and Operate Machinery

Metoclopramide can cause drowsiness or 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.

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

Reproduction studies performed in rats, mice and rabbits by the IM, IV, subcutaneous (SC), 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.

Fetal/Neonatal Adverse Reactions

Metoclopramide crosses the placental barrier and may cause extrapyramidal signs and methemoglobinemia in neonates with material administration during delivery. Monitor neonates for extrapyramidal signs.

Nursing Mothers

Metoclopramide is excreted in human milk. C Monitor breastfeeding neonates because metoclopramide may cause extrapyramidal signs (dystonias) and methemoglobinemia.

Pediatric Use

The safety and effectiveness of REGLAN Injection has been established as a single dose to facilitate small bowel intubation in pediatric patients in whom the tube does not pass the pylorus with conventional maneuvers.

The safety and effectiveness of REGLAN Injection has not been established in pediatric patients for the following:

- relief of symptoms associated with diabetic gastroparesis
- prevention of nausea and vomiting associated with emetogenic cancer chemotherapy
- prevention of postoperative nausea and vomiting
- to stimulate gastric emptying and intestinal transit of barium where delayed emptying interferes with radiological examination of the stomach and/or small intestine.

The safety profile of metoclopramide in adults cannot be extrapolated to pediatric patients. Neonates have reduced levels of NADH-cytochrome b_5 reductase which, make neonates more susceptible to methemoglobinemia (see **OVERDOSAGE**). 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

Metoclopramide is known to be substantially excreted by the kidney, and the risk of adverse reactions, including TD, may be greater in patients with impaired renal function (see **WARNINGS – Tardive Dyskinesia**).

The risk of developing parkinsonian-like side effects increases with ascending dose. Geriatric patients should receive the lowest dose of REGLAN Injection that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving REGLAN Injection, REGLAN Injection should generally be discontinued before initiating any specific anti-parkinsonian agents (see **WARNINGS – Other Extrapyramidal Symptoms).**

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

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 - Use in Patients with Renal or Hepatic Impairment**).

Other Special Populations

NADH-Cytochrome b5 Reductase Deficiency

Patients with NADH-cytochrome b_5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended (see **OVERDOSAGE**).

CYP2D6 Poor Metabolizers

Metoclopramide is a substrate of CYP2D6. The elimination of metoclopramide may be slowed in patients who are CYP2D6 poor metabolizers (compared to patients who are CYP2D6 intermediate, extensive , or ultra-rapid metabolizers); possibly increasing the risk of dystonic and other adverse reactions to REGLAN Injection. Avoid REGLAN Injection in patients who are poor CYP2D6 metabolizers. If use in unavoidable, monitor for adverse reactions.

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 may occur in patients receiving the recommended prescribed dosage of REGLAN Injection. Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation also may occur (see **WARNINGS**). In cancer chemotherapy patients being treated with 1-2 mg/kg per dose, incidence of drowsiness is about 70%. There are isolated reports of convulsive seizures without 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. In cancer chemotherapy patients receiving 1-2 mg/kg per dose, the incidence is 2% in patients over the ages of 30-35, and 25% or higher in pediatric patients and adult patients less than 30 years of age who have not had prophylactic administration of diphenhydramine. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (tetanus-like reactions), and, rarely, stridor and dyspnea possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine (see **WARNINGS**).

Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies (see **WARNINGS**).

Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth, or jaw, and sometimes by involuntary movements of the trunk and/or extremities; movements may be choreoathetotic in appearance (see **WARNINGS**).

Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing, foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

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, muscular rigidity, altered consciousness, and autonomic instability (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 atrioventricular (AV) block (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Gastrointestinal
Nausea and bowel disturbances, primarily diarrhea.

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

Renal
Urinary frequency and incontinence.

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

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

Miscellaneous
Visual disturbances. Porphyria.

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

OVERDOSAGE
Manifestations of metoclopramide overdosage included drowsiness, disorientation, extrapyramidal reactions, other adverse reactions associated with metoclopramide use (including, e.g., methemoglobinemia), and sometimes death. Neuroleptic malignant syndrome (NMS) has been reported in association with metoclopramide overdose and concomitant treatment with another drug associated with NMS (see **WARNINGS**).

There are no specific antidotes for REGLAN Injection overdosage. If over-exposure occurs, call your Poison Control Center at 1-800-222-1222 for current information on the management of poisoning or overdosage.

Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, which may be fatal.

Hemodialysis and continuous ambulatory peritoneal dialysis do not remove significant amounts of metoclopramide.

DOSAGE AND ADMINISTRATION

For the Relief of Symptoms Associated with Diabetic Gastroparesis

If only the earliest manifestations of diabetic gastroparesis are present, oral administration of metoclopramide may be initiated. However, if severe symptoms are present, the recommended dosage of REGLAN Injection in adults is 10 mg administered intramuscularly or intravenously over at least 1- to 2-minutes.

Administration of REGLAN Injection up to 10 days may be required before symptoms subside, at which time oral administration of metoclopramide may be instituted.

Avoid a total duration of treatment with metoclopramide products, including REGLAN Injection, for longer than 12 weeks. If longer-term use us unavoidable, routinely monitor for signs and symptoms of TD (see **WARNINGS – Tardive Dyskinesia**).

For the Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy

The recommended dosage of REGLAN Injection in adults is 2 mg/kg, with highly emetogenic drugs (e.g., cisplatin or dacarbazine) alone or in combination, and 1 mg/kg, with less emetogenic drugs, infused intravenously over at least 15 minutes, 30 minutes before beginning cancer chemotherapy and repeated every 2 hours for two doses, then every 3 hours for three doses.

For doses in excess of 10 mg, REGLAN Injection should be diluted in 50 mL of a parenteral solution.

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

If acute dystonic reactions should occur, inject 50 mg Benadryl® (diphenhydramine hydrochloride) intramuscularly, and the symptoms usually will subside.

For the Prevention of Postoperative Nausea and Vomiting

The recommended dosage of REGLAN Injection in adults is 10 mg or 20 mg as a single intramuscular injection near the end of surgery.

To Facilitate Small Bowel Intubation

In adult and pediatric patients undergoing small bowel intubation, in whom the tube has not passed the pylorus with conventional maneuvers after 10 minutes, the recommended dosage of REGLAN Injection is a single dose administered (undiluted) by the intravenous route over at least 1 to 2 minutes:

- *Adults and pediatric patients above 14 years of age*: 10 mg

- *Pediatric patients 6 to 14 years of age*: 2.5 to 5 mg
- *Pediatric patients less than 6 years of age*: 0.1 mg/kg

To Aid in Radiological Examinations

In adult patients where delayed gastric emptying interferes with radiological examination of the stomach and/or small intestine, the recommended dosage of REGLAN Injection is a single 10 mg dose administered (undiluted) by the intravenous route over at least 1- to 2-minutes.

Use in Patients with Renal Impairment

The clearance of metoclopramide is decreased, and the systemic exposure is increased in patients with moderate to severe renal impairment compared to patients with normal renal function, which may increase the risk of adverse reactions.

There is no dosage adjustment for patients with mild renal impairment (creatinine clearance greater than 60 mL/minute).

For patients with moderate or severe renal impairment (creatinine clearance less than or equal to 60 mL/minute), who are receiving more than a single dose of REGLAN Injection, reduce the REGLAN Injection dosage to one-half the dosage recommended for patients with normal renal function.

For patients with End-Stage Renal Disease (ESRD) including those treated with hemodialysis or continuous ambulatory peritoneal dialysis, who are receiving more than a single dose of REGLAN Injection, reduce the REGLAN Injection dosage to one-fourth the dosage recommended for patients with normal renal function.

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

Use in Patients with Hepatic Impairment

Patients with severe hepatic impairment (Child-Pugh C) have reduced systemic metoclopramide clearance (by approximately 50%) following intravenous administration compared to patients with normal hepatic function. The resulting increase in metoclopramide blood concentrations increases the risk of adverse reactions. There is no pharmacokinetic data in patients with moderate hepatic impairment (Child-Pugh B).

There is no dosage adjustment required for patients with mild hepatic impairment (Child-Pugh A). For patients with moderate and severe hepatic impairment (Child-Pugh B or C), who are receiving more than a single dose of REGLAN Injection, reduce the REGLAN Injection dosage to one-half the dosage recommended for patients with normal hepatic function.

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

ADMIXTURES COMPATIBILITIES

REGLAN Injection is compatible for mixing and injection with the following dosage forms to the extent indicated below:

Physically and Chemically Compatible Up to 48 Hours

Cimetidine Hydrochloride (SK&F), Mannitol, USP (Abbott), Potassium Acetate, USP (Invenex), Potassium Phosphate, USP (Invenex).

Physically Compatible Up to 48 Hours

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

Physically Compatible Up to 24 Hours

(Do not use if precipitation occurs)

Clindamycin Phosphate, USP (Upjohn), Cyclophosphamide, USP (Mead-Johnson), Insulin, USP (Lilly).

Conditionally Compatible

(Use within one hour after mixing or may be infused directly into the same running IV line)

Ampicillin Sodium, USP (Bristol), Cisplatin (Bristol), Erythromycin Lactobionate, USP (Abbott), Methotrexate Sodium, USP (Lederle), Penicillin G Potassium, USP (Squibb), Tetracycline Hydrochloride, USP (Lederle).

Incompatible

(Do Not Mix)

Cephalothin Sodium, USP (Lilly), Chloramphenicol Sodium, USP (Parke-Davis), Sodium Bicarbonate, USP (Abbott).

HOW SUPPLIED

REGLAN Injection (metoclopramide injection, USP) 5 mg metoclopramide base (as the monohydrochloride monohydrate) per mL; available in:

2 mL single dose vials in cartons of 25 (NDC xxxxxx),

10 mL single dose vials in cartons of 25 (NDC xxxxxx),

30 mL single dose vials in cartons of 25 (NDC xxxxxxxx).

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

Metoclopramide base (as the monohydrochloride monohydrate)

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

This product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

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

REGLAN Injection should be stored at Controlled Room Temperature, 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

For Product Inquiry call 1-877-845-0689.

Manufactured by:

Hikma Pharmaceuticals USA Inc.

Berkeley Heights, NJ 07922

Revised February 2026
MLT00066,J

MEDICATION GUIDE
REGLAN (Reg-lan)
(metoclopramide)
injection

You or your caregiver should read the Medication Guide before you start receiving REGLAN Injection and before you get another dose of REGLAN Injection. There may be new information. If you take another product that contains metoclopramide (such as tablets, orally disintegrating tablets, oral syrup, or nasal spray), 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 to your doctor about your medical condition or your treatment.

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

REGLAN Injection can cause serious side effects, including:

Tardive Dyskinesia:
Metoclopramide, including REGLAN Injection, can cause tardive dyskinesia (TD), a potentially irreversible serious movement disorder.

- These movements happen mostly in the face or tongue, and sometimes in the arms or legs. You cannot control these movements.
- These symptoms may not go away even after stopping REGLAN Injection.

Your chances for getting TD go up:

- the longer you take REGLAN Injection and the more REGLAN Injection you take. People taking REGLAN Injection to relieve the symptoms of slow stomach emptying due to diabetes, should not take REGLAN Injection, or other drugs containing metoclopramide, for more than 12 weeks.
- if you are older, especially if you are a woman.
- if you have diabetes.

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

Call your doctor right away if you get movements you cannot 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

Your doctor may stop treatment with REGLAN Injection if you develop signs or symptoms of TD.

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

What is REGLAN Injection?

REGLAN Injection is a prescription medicine used to:

- relieve symptoms of slow stomach emptying in adults with diabetes.
- prevent nausea and vomiting that can happen with cancer chemotherapy in adults.
- prevent nausea and vomiting that may happen after surgery in adults, if your doctor decides that you should not be treated with a stomach tube and suction.
- help make it easier to insert a tube into the small intestine in both adults and children, if the tube does not pass into the stomach normally.
- to help empty stomach contents or to help barium move through the intestine in adults, when you get an X-ray examination of the stomach or small intestine.

It is not known if REGLAN Injection is safe and effective in children **except** when used to help insert a tube into the small intestine.

Who should not receive REGLAN Injection?

Do not receive REGLAN Injection if you:

- have a history of tardive dyskinesia or have a problem controlling your muscles and movements after taking REGLAN Injection or a medicine that works like REGLAN Injection.
- have stomach or intestine problems that could get worse with REGLAN Injection, such as bleeding, blockage or a tear in your stomach or bowel wall.
- have an adrenal gland tumor called pheochromocytoma.
- are allergic to metoclopramide.
- have seizures.

What should I tell my doctor before receiving REGLAN Injection?

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

- have problems controlling your muscle movements after taking any medicine.
- have Parkinson's disease.
- have or had depression or mental illness.
- have kidney or liver problems.
- have heart failure failure or heart rhythm problems.
- have high blood pressure.
-
- drink alcohol.
- have diabetes. Your dose of insulin may need to be changed.
- are pregnant or plan to become pregnant. It is not known if REGLAN Injection will harm your unborn child.
- are breastfeeding. REGLAN Injection is passed into human milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you take REGLAN Injection.

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

Especially tell your doctor if you take:

- another medicine that contains metoclopramide, such as metoclopramide tablets, metoclopramide orally disintegrating tablets, metoclopramide oral syrup, or Gimoti nasal spray
- an anti-psychotic medicine, used to treat mental illness such as schizophrenia
- a medicine for Parkinson's disease
- a medicine for depression, especially a Monoamine Oxidase Inhibitor (MAOI)
- insulin
- medicines that can make you sleepy, such as anti-anxiety medicines, sleep medicines, and narcotics.

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist. Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How will I receive REGLAN Injection?

- REGLAN Injection will be given to you by intravenous (IV) infusion into your vein or by intramuscular (IM) injection into a large muscle. Where and how you receive your REGLAN injection (IV or IM) will depend on why you are receiving it.
- Certain side effects can happen if REGLAN Injection is given too fast. See the section "What are the possible side effects of REGLAN Injection?"
- You should not take or receive medicines containing metoclopramide (including REGLAN Injection) for more than 12 weeks.

What should I avoid while receiving REGLAN Injection?

- Do not drink alcohol while receiving REGLAN Injection. Alcohol may make some side effects of REGLAN Injection worse, such as feeling sleepy.
- Do not drive, work with machines, or do dangerous tasks until you know how REGLAN Injection affects you. REGLAN Injection may cause sleepiness.
- You should avoid taking antipsychotic medicines (used to treat mental illness such as schizophrenia), while receiving REGLAN Injection. Taking these medicines with REGLAN Injection may make the serious side effect TD worse.

What are the possible side effects of REGLAN Injection?

REGLAN Injection can cause serious side effects, including:

- **Tardive dyskinesia (Abnormal muscle movements).** See the section "**What is the most important information I should know about REGLAN Injection?**"

- **Uncontrolled spasms of your face and neck muscles, or muscles of your body, arms, and legs (dystonia).** These muscle spasms can cause abnormal movements and body positions. These spasms usually start within the first 2 days of treatment. These spasms happen more often in children and adults under age 30 and in those who took higher doses of metoclopramide.

- **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 Injection.

- **Being unable to sit still or feeling you need to move your hands, feet, or body (akathisia).** Symptoms can include feeling jittery, anxious, irritated or unable to sleep (insomnia), feeling the need to walk around (pacing) and tapping your feet.

- **Neuroleptic Malignant Syndrome (NMS).** NMS is a very rare but very serious condition that can happen with REGLAN Injection. 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.

- **Depression, thoughts about suicide, and suicide.** Some people who take REGLAN Injection become depressed. You may have thoughts about hurting or killing yourself. Some people who take REGLAN Injection have ended their own lives (suicide).

- **High blood pressure.** REGLAN Injection can cause your blood pressure to increase.

- **Too much body water.** People who have certain liver problems or heart failure and take REGLAN Injection may hold too much water in their body (fluid retention). Tell your doctor right away if you have sudden weight gain, or swelling of your hands, legs, or feet.

Call your doctor and get medical help right away if you:
- have muscle movements you cannot stop or control
- have muscle movements that are new or unusual
- 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

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

Infusion related side effects can happen if REGLAN Injection is given too fast. You may feel very anxious and restless for a short time, and then become sleepy while you are receiving a dose of REGLAN Injection. Tell your doctor or nurse right away if this happens.

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

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 Injection.

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

General information about REGLAN Injection

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about REGLAN Injection. If you would like more information about REGLAN Injection, talk with your doctor. You can ask your doctor or pharmacist for information about REGLAN Injection that is written for healthcare professionals. For more information, call Baxter Healthcare at 1-800-933-3030.

What are the ingredients in REGLAN injection?
Active ingredient: metoclopramide
Inactive ingredients: sodium chloride, water, hydrochloric acid or sodium hydroxide

Revised February 2026
Manufactured by:
Manufactured by:

Hikma Pharmaceuticals USA Inc.

Berkeley Heights, NJ 07922

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