CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-246

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

METOZOLV ODT (metoclopramide hydrochloride) orally disintegrating tablets

Initial U.S. Approval: 1976

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. The risk of developing tardive dyskinesia increases with the duration of treatment and the 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. *(5.1)*

------INDICATIONS AND USAGE------

METOZOLV ODT is a dopamine receptor antagonist indicated for:

- **Relief of 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 in adults associated with acute and recurrent diabetic gastroparesis (gastric stasis) (1.2)

Important Limitations:

- Therapy should not exceed 12 weeks in duration (1.3)
- METOZOLV ODT is recommended only for adults. The safety and effectiveness in pediatric patients have not been established (1.3)

------DOSAGE AND ADMINISTRATION------

- **Gastroesophageal Reflux Disease:** 10 mg to 15 mg dose up to four times daily at least 30 minutes before eating and at bedtime (2.2)
- **Diabetic Gastroparesis (Diabetic Gastric Stasis):** 10 mg dose four times daily at least 30 minutes before eating and at bedtime for two to eight weeks (2.3)

-------DOSAGE FORMS AND STRENGTHS------

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

------CONTRAINDICATIONS------

- Intestinal Obstruction, Hemorrhage, or Perforation (4.1)
- Pheochromocytoma (4.2)
- Known Sensitivity or Intolerance (4.3)
- Epilepsy (4.4)
- Concomitant Medications with Extrapyramidal Reactions (4.5)

------WARNINGS AND PRECAUTIONS------

- Tardive Dyskinesia (5.1)
- Acute Dystonic Reactions, Drug-induced Parkinsonism and Other Extrapyramidal Symptoms (5.2)
- Neuroleptic Malignant Syndrome (5.3)
- Depression (5.4)
- Hypertension (5.5)
- Congestive Heart Failure and Ventricular Arrhythmia (5.6)
- Withdrawal from Metoclopramide (5.7)

------ADVERSE REACTIONS------

The most common adverse reactions (>2%) are headache, nausea, vomiting, fatigue, and somnolence.(6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-508-0024 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

------DRUG INTERACTIONS------

- Anticholinergic drugs: Antagonize 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 and increase absorption of drugs from the small bowel (7.3)
- Insulin: Changes in food transit time may require adjustment of insulin dose or timing to avoid hypoglycemia (7.4)
- Antidepressants, Antipsychotics, and Neuroleptics: Concomitant use with metoclopramide is associated with increased risk of tardive dyskinesia and Neuroleptic Malignant Syndrome (7.5)

------ USE IN SPECIFIC POPULATIONS------

- Pediatric Use: The safety and effectiveness of METOZOLV ODT 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)
- Impaired Renal Function: Initial dosing may need to be reduced and titrated (8.6).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: xx/xx

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

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

1.1 Symptomatic Gastroesophageal Reflux Disease

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

1.2 Diabetic Gastroparesis (Diabetic Gastric Stasis)

METOZOLV ODT is indicated for the relief of symptoms associated with acute and recurrent diabetic gastroparesis (gastric stasis) in adults.

1.3 Important Limitations

METOZOLV 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

2.1 Important Instructions for Use

Take on an empty stomach at least 30 minutes before eating since food can decrease the peak concentrations of drug in the bloodstream and/or the time it takes to achieve the maximum drug level in the bloodstream *[see Clinical Pharmacology (12.3)]*. Do not repeat dose if inadvertently taken with food.

Since the tablet absorbs moisture rapidly, only remove each dose from the packaging just prior to taking. Handle the tablet with dry hands and place on the tongue. If the tablet should break or crumble while handling, discard and remove a new tablet.

Metozolv ODT disintegrates on the tongue in approximately one minute (with a range of 10 seconds to 14 minutes). METOZOLV ODT is designed to be taken without liquid; however, the effect on the pharmacokinetics of taking METOZOLV ODT with liquid is unknown.

2.2 Symptomatic Gastroesophageal Reflux Disease

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

Take 10 mg to 15 mg dose of METOZOLV ODT up to four times daily (e.g., at least 30 minutes before each meal and at bedtime). Doses may vary depending upon the symptoms being treated and the clinical response. If symptoms only occur intermittently or at specific times of the day, metoclopramide may be used in single doses up to 20 mg prior to the symptoms rather than continuous treatment.

Since there is a poor correlation between symptomatic relief and healing of esophageal lesions, any therapy directed at esophageal lesions is best confirmed by endoscopic evaluation. Although experience with the effects of metoclopramide on esophageal erosions and ulcerations is limited, healing was documented in a controlled trial using four times daily therapy at 15 mg/dose. 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.

Take a 10 mg dose of METOZOLV ODT up to four times a day (e.g., at least 30 minutes before each meal and at bedtime).

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 METOZOLV ODT may be initiated. However, if severe symptoms are present, therapy should begin with metoclopramide injection.

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, METOZOLV ODT therapy should be reinstituted at the earliest manifestation.

2.4 Renal Impairment

Some patients, such as the elderly or those with impaired kidney function (creatinine clearance 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.

3 DOSAGE FORMS AND STRENGTHS

5 mg Tablets: Each white round 5 mg tablet is debossed with "5" on one side and plain on the other.

10 mg Tablets: Each white round 10 mg tablet is debossed with "10" on one side and plain on the other.

4 CONTRAINDICATIONS

4.1 Intestinal Obstruction, Hemorrhage, or Perforation

Do not use Metoclopramide whenever stimulation of gastrointestinal motility may be dangerous such as in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

4.2 Pheochromocytoma

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may precipitate a hypertensive crisis, most likely 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

Do not use Metoclopramide in patients with epilepsy since the frequency and severity of seizures may be increased.

4.5 Concomitant Medications with Extrapyramidal Reactions

Do not use Metoclopramide in patients receiving other drugs which 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 (6.2) and Drug Interactions (7.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Tardive Dyskinesia

Treatment with metoclopramide can cause tardive dyskinesia (TD) *[see Boxed Warning]*, 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 (EPS), 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 occur, inject 50 mg diphenhydramine hydrochloride intramuscularly. Benztropine mesylate, 1 to 2 mg intramuscularly, may also be used to reverse these reactions.

Drug-induced Parkinsonism can occur during metoclopramide therapy, more commonly within the first 6 months after beginning treatment, but also after longer periods. Parkinsonian symptoms generally subside within 2 to 3 months following discontinuation of metoclopramide. Patients with a history of Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients can experience exacerbation of Parkinsonian symptoms when taking metoclopramide.

5.3 Neuroleptic Malignant Syndrome

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) 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 immediate discontinuation of metoclopramide and other

drugs not essential to concurrent therapy; intensive symptomatic treatment and medical monitoring; and, 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 has not been established *[see Adverse Reactions (6)]*.

5.4 Depression

Depression associated with metoclopramide use has occurred in patients with and without a history of depression. Symptoms ranged from mild to severe and included suicidal ideation and suicide. For those patients with a prior history of depression, metoclopramide should only be given 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 METOZOLV 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

Since metoclopramide produces a transient increase in plasma aldosterone, patients 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 in any patients 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 METOZOLV ODT. A small number of patients may experience withdrawal symptoms after stopping that could include dizziness, nervousness, and/or headaches.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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 studies of another drug and may not reflect the rates observed in clinical practice.

A total of 86 subjects entered three studies with METOZOLV ODT; 12 subjects entered a pilot bioavailability study (BA); 44 subjects entered a bioequivalence (BE) study, and 30 subjects entered a food-effect study. The adverse reactions from the BE and food-effect study are summarized in Table 1. The pilot BA study data are not included because it was performed with a formulation different from the METOZOLV ODT formulation.

The adverse experience profile seen with METOZOLV ODT was similar to metoclopramide tablets. Thirty-three (33) adverse reactions were reported after receiving METOZOLV ODT and 30 adverse reactions were reported after receiving metoclopramide tablets.

Table 1: Adverse Reactions in BE and Food-Effect Study in ≥ 2% of Subjects

Adverse Reaction	**METOZOLV ODT** N[1] (%) [2]	**Metoclopramide tablets** N[1] (%) [2]
Nausea	4 (4.2 %)	4 (5.6 %)
Vomiting	2 (2.1 %)	1 (1.4 %)
Fatigue	2 (2.1 %)	2 (2.8 %)
Headache	5 (5.2 %)	3 (4.2 %)
Somnolence	2 (2.1 %)	2 (2.8 %)

Dizziness	1 (1.0 %)	3 (4.2 %)	213

[1] N = number of subjects that reported adverse reactions
[2] Percent (%) occurrence = N divided by number of subjects dosed with respective study drug
[3] Number of subjects dosed with METOZOLV ODT: 68 under fasted conditions and 28 under fed conditions.
[4] Number of subjects dosed with metoclopramide tablets: 28 under fed conditions and 44 under fasted conditions.

The most frequently reported adverse reactions (greater than 2%) associated with METOZOLV ODT were: nausea, vomiting, fatigue, somnolence and headache. The most frequently reported adverse reactions (greater than 2%) associated with metoclopramide tablets were: nausea, headache, fatigue, somnolence, and dizziness. The combined data from the fasted BE study and the food-effect study did not demonstrate any significant differences in the adverse event profile for METOZOLV ODT compared to metoclopramide tablets.

6.2 Post-Marketing Experience

The following adverse reactions are from the cumulative post-marketing experience with metoclopramide tablets. Since the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

CNS Effects: Restlessness, drowsiness, fatigue, and lassitude occur in approximately 10% of patients receiving the most commonly prescribed dosage of 10 mg four times a day. Insomnia, headache, confusion, dizziness, or depression with suicidal ideation occurs less frequently. The incidence of drowsiness is greater at higher doses. There are isolated reports of seizures without clear-cut relationship to metoclopramide. Rarely, hallucinations have been reported.

Extrapyramidal Syndromes (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 (5.1)*].

Drug-induced parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies [see *Warnings and Precautions (5.2)*].

Tardive dyskinesia is most frequently 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. Motor restlessness (akathisia) may include inability to sit still, pacing, and 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 *[see Warnings and Precautions (5.3)]*.

Endocrine Disturbances: Galactorrhea, amenorrhea, gynecomastia, and impotence secondary to hyperprolactinemia. Fluid retention secondary to transient elevation of aldosterone.

Cardiovascular: Hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention, acute congestive heart failure, possible AV block.

Gastrointestinal: Nausea, 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. 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

Metoclopramide has been shown to release catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients taking monoamine oxidase (MAO) inhibitors.

7.3 Drug absorption

Absorption of drugs from the stomach may be diminished by metoclopramide (e.g., digoxin), 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

Because the action of metoclopramide will hasten the movement of food to the intestines and therefore the rate of absorption, insulin dosage or timing of dosage may require adjustment. 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.

7.5 Antidepressants, antipsychotics, and neuroleptics

Concomitant use of metoclopramide should be avoided in patients taking antidepressants, antipsychotics, and/or neuroleptics that have been associated with extrapyramidal reactions such as tardive dyskinesia or Neuroleptic Malignant Syndrome (NMS) that have occurred in association with metoclopramide *[see Warnings and Precautions (5.2), (5.3) and Adverse Reactions (6.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category B

Reproduction studies have been performed in rats at oral doses about 6 times the maximum recommended human dose calculated on the basis of surface area, and in rabbits at oral doses about 12 times the maximum recommended human dose calculated on the basis of surface area, 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 from metoclopramide in nursing infants and

because of the potential for tumorigenicity (including tumor promoting potential 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

The safety and effectiveness of METOZOLV ODT in pediatric patients have not been established.

The safety profile of METOZOLV ODT 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. In addition, neonates have reduced levels of NADH-cytochrome b5 reductase making them more susceptible to methemoglobinemia, a possible side effect of metoclopramide use in neonates.

Pediatric PK

The pharmacodynamics of metoclopramide following oral and intravenous administration in pediatric populations are highly variable and a concentration-effect relationship has not been established. Thus, there are insufficient data to conclude whether the pharmacokinetics of Metozolv ODT 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 disease (GERD) or cancer chemotherapy-related nausea and vomiting, the pharmacokinetics of metoclopramide have been studied in these patient populations and are summarized as follows.

In an open-label study, six pediatric patients (ranging in age from 3.5 weeks to 5.4 months) with GERD 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 twice the level (56.8 mcg/L) compared to after the first dose (29 mcg/L) indicating drug accumulation with repeated dosing. However, the PK parameters after the tenth dose were comparable to those observed after the first dose for 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). The youngest patient (3.5 weeks) showed a significantly longer half-life after the first dose (23.1 hr) compared to after the tenth dose (10.3 hr), suggesting the reduced clearance observed at birth may be a reflection of the immature hepatic and renal systems.

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 drug-induced parkinsonism due to metoclopramide is dose-related. Geriatric patients should receive the lowest dose that is effective. If drug-induced parkinsonism symptoms develop in a geriatric patient, METOZOLV ODT should be discontinued. The elderly may be at greater risk for tardive dyskinesia [see *Warnings and Precautions* (5.1)].

Sedation is a potential adverse event associated with metoclopramide use in the elderly.

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. For these reasons, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, due to the greater frequency of decreased renal function, concomitant disease, or other drug therapy in the elderly. *[see Warnings and Precautions (5.4)]*.

8.6 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.

Since metoclopramide is excreted principally through the kidneys, therapy should be initiated at approximately one-half the recommended dose in those patients whose creatinine clearance is below 40 mL/min. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate. Metoclopramide has been safely used in patients with advanced liver disease whose renal function was normal.

10 OVERDOSAGE

Symptoms of overdosage may include drowsiness, disorientation, and extrapyramidal reactions. Anticholinergic or anti-Parkinson drugs or antihistamines with anti-cholinergic 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 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.

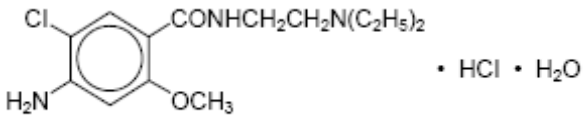
Methemoglobinemia has occurred in premature and full-term neonates who were given overdoses of metoclopramide (1 to 4 mg/kg/day orally, intramuscularly or intravenously for 1 to 3 or more days). Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene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

11 DESCRIPTION

METOZOLV ODT is an orally disintegrating tablet formulation of metoclopramide hydrochloride. The 5 mg strength is a round white tablet debossed on one side with a "5" and plain on the other side; it is comprised of 5 mg metoclopramide (as 5.91 mg of metoclopramide hydrochloride) with gelatin, mannitol, mint flavoring, and Acesulfame K (artificial sweetener). The 10 mg strength is a round white tablet debossed on one side with a "10" and plain on the other side; it is comprised of 10 mg metoclopramide (as 11.82 mg of metoclopramide hydrochloride) with gelatin, mannitol, mint flavoring, and Acesulfame K.

The active ingredient, metoclopramide hydrochloride, is a white crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its molecular formula is $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$. Its molecular weight is 354.3. The structural formula is shown in Figure 1.

Figure 1



METOZOLV ODT includes the following inactive ingredients: gelatin, mannitol, mint flavoring, Acesulfame Potassium (artificial sweetener), and trace amounts of sodium chloride and sodium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. While its mode of action is unclear, it appears to sensitize tissues to the action of acetylcholine. The effect on motility is not dependent on intact vagal innervation, but 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 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 *[see Warnings and Precautions (5.2), (5.3)]*.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 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 a 20 mg dose lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

The principal effect of metoclopramide is on symptoms of post-prandial 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 taken four times a day. As there is no documented correlation between symptoms and healing of esophageal lesions, patients with documented lesions should be monitored endoscopically. For gastroparesis, the usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) appear to respond within different time intervals.

12.3 Pharmacokinetics

Adult PK of METOZOLV ODT

In a randomized, two-arm, two-way crossover study in 44 healthy adult (male and female) fasted subjects, METOZOLV ODT was bioequivalent to Reglan Tablets.

In a food-effect study with 28 subjects, METOZOLV ODT taken immediately after a high-fat meal had a 17% lower peak blood level than when taken after an overnight fast. The time to peak blood levels increased from about 1.75 hours under fasted conditions to 3 hours when taken immediately after a high fat meal. The extent of metoclopramide absorbed (area under the curve) was comparable whether METOZOLV ODT was administered with or without food. The clinical effect of the decrease in peak plasma level if Metozolv ODT is inadvertently taken with food is unknown.

Adult PK of Metoclopramide

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 to 2 hr after a single oral dose. Similar time to peak is observed after individual doses at steady state. A single dose study of 12 subjects showed that the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg (results summarized in Table 2). Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5 to 6 hr. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

Table 2: Adult Pharmacokinetic Data

Parameter	Value
Vd (L/kg)	~ 3.5
Plasma Protein Binding	~ 30%
T ½	5 to 6 hours
Oral Bioavailability	80% ± 15.5%

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.

The in-*vivo* disintegration time (time reported between placing the tablet on the tongue and it completely disintegrated into fine particles) was approximately one minute (with a range of 10 seconds to 14 minutes). In the two clinical trials (N = 96) with a mean ± SD being 76.8 ± 110.6 seconds and a median of 53.5 seconds.

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. The reduction in clearance as a result of renal impairment suggests that reduction of maintenance dosage should be done to avoid drug accumulation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 77-week study was conducted in rats with oral doses 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 based on body surface area) 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 (about 3 times the maximum recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

16 HOW SUPPLIED/STORAGE AND HANDLING

5 mg Tablets: Available in blister pack with 10 tablets individually sealed in a foil-backed unit-dose container; a carton contains 10 cards (NDC 65649-431-02).

10 mg Tablets: Available in blister pack with 10 tablets individually sealed in a foil-backed unit-dose container; a carton contains 10 cards (NDC 65649-432-02).

Tablets should be stored at controlled room temperature, between 20°C and 25°C (68°F and 77°F).

17 PATIENT COUNSELING INFORMATION

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

- A patient Medication Guide is available for METOZOLV ODT and printed at the end of the prescribing information. Instruct patients, families, and caregivers to read the Medication Guide and assist them in understanding its contents.
- 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 METOZOLV ODT.
- Inform patients that METOZOLV ODT may cause drowsiness, dizziness, or otherwise impair mental alertness 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.
- Inform patients that the most common adverse reactions in patients treated with METOZOLV ODT or other metoclopramide-containing products are headache, nausea, vomiting, tiredness, sleepiness, dizziness, and restlessness.

Manufactured by:
Catalent UK Swindon Zydis Limited
Swindon, UK

Manufactured for:
Salix Pharmaceuticals, Inc.
Morrisville, North Carolina

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(metoclopramide hydrochloride)
Orally Disintegrating Tablets

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METOZOLV ODT can cause serious side effects, including:

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

Your chances for getting TD go up:
- the longer you take METOZOLV ODT and the more METOZOLV ODT you take. You should not take METOZOLV ODT for more than 12 weeks.
- if you are older, especially if you are an older woman
- if you have diabetes

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

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

- lip smacking, chewing, or puckering of your lips
- 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 METOZOLV ODT?" for more information about side effects.

What is METOZOLV ODT?

METOZOLV ODT is a prescription medicine used in adults:

- for 4 to 12 weeks to relieve heartburn symptoms of gastroesophageal reflux disease (GERD) when certain other treatments do not work.
- to relieve the symptoms of slow stomach emptying in people with diabetes.

It is not known if METOZOLV ODT is safe or works in children.

Who should not take METOZOLV ODT?

Do not take METOZOLV ODT if you:

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

What should I tell my doctor before taking METOZOLV ODT?

Before you take METOZOLV ODT, tell your doctor if you:

- have kidney or liver disease
- have depression or mental illness
- have high blood pressure
- have heart failure or heart rhythm problems
- have diabetes. Your dose of insulin may need to be changed.
- have Parkinson's disease
- have any other medical conditions
- drink alcohol
- are pregnant or plan to become pregnant. It is not known if METOZOLV ODT will harm your unborn baby.
- are breast-feeding or plan to breast-feed. METOZOLV ODT can pass into your milk and may harm your baby. You and your doctor should decide if you will take METOZOLV ODT or breast-feed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. METOZOLV ODT and some medicines can affect each

other and may not work as well, or cause possible side effects. Do not start any new medicine while taking METOZOLV ODT until you talk with your doctor.

Especially tell your doctor if you take:

• another medicine that contains metoclopramide, such as REGLAN tablets, REGLAN ODT, or metoclopramide oral syrup
• a blood pressure medicine
• a medicine for depression, especially a monoamine oxidase inhibitor (MAOI)
• an anti-psychotic medicine
• insulin
• medicines that can make you sleepy, such as anti-anxiety medicines, sleep medicines, and narcotics.

Ask your doctor or pharmacist if you are not sure if your medication is listed above.

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

How should I take METOZOLV ODT?

• METOZOLV ODT comes as a tablet that melts in your mouth.
• Take METOZOLV ODT exactly as prescribed by your doctor. Do not change your dose unless your doctor tells you to.
• You should not take METOZOLV ODT for more than 12 weeks.
• Take METOZOLV ODT at least 30 minutes before eating and at bedtime.

To take METOZOLV ODT:

1. Leave the tablet in the sealed blister METOZOLV ODT pack until you are ready to take it.
2. Use dry hands to open a blister and take out a tablet. If the tablet breaks or crumbles throw it away and take a new tablet out of the blister pack.
3. Put the tablet on your tongue right away. Let it melt and then swallow. You do not need water to take METOZOLV ODT.

If you take too much METOZOLV ODT, call your doctor or Poison Control Center.

What should I avoid while taking METOZOLV ODT?

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

What are the possible side effects of METOZOLV ODT?

METOZOLV ODT can cause serious side effects, including:

• **Abnormal muscle movements.** See "What is the most important information I should know about METOZOLV ODT?"

• **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 younger than 30.

• **Depression, thoughts about suicide, and suicide.** Some people who take METOZOLV ODT may become depressed. You may have thoughts about hurting or killing yourself. Some people who have taken metoclopramide products have ended their own lives (suicide).

• **Neuroleptic Malignant Syndrome (NMS).** NMS is a rare but very serious condition that can happen with METOZOLV 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 have Parkinson's Disease, your symptoms may become worse while you are taking METOZOLV ODT.

• **High blood pressure.** METOZOLV ODT can cause your blood pressure to increase.

• **Too much body water.** People who have certain liver problems or heart failure and take METOZOLV ODT 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:

- 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 cannot stop or control
- have muscle movements that are new or unusual

The most common side effects of METOZOLV ODT are:

- headache
- nausea
- vomiting
- tiredness
- sleepiness

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

You may still have side effects after you stop METOZOLV ODT. You may have symptoms from stopping (withdrawal) METOZOLV 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 METOZOLV 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 METOZOLV ODT?

- Store METOZOLV ODT at room temperature, between 68° F to 77° F (20°C to 25°C).
- Keep METOZOLV ODT away from moisture.
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Keep METOZOLV ODT and all medicines away from children.

General information about METOZOLV ODT

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What are the ingredients in METOZOLV ODT?

Active ingredients: metoclopramide hydrochloride
Inactive ingredients: gelatin, mannitol, mint flavoring, acesulfame potassium (artificial sweetener), and trace amounts of sodium chloride and sodium hydroxide

Salix Pharmaceuticals, Inc.
Morrisville, NC 27560, USA

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

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