METOCLOPRAMIDE HYDROCHLORIDE- metoclopramide hydrochloride tablet, orally disintegrating
Lupin Pharmaceuticals,Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use METOCLOPRAMIDE hydrochloride safely and effectively. See full prescribing information for METOCLOPRAMIDE hydrochloride.

METOCLOPRAMIDE orally disintegrating tablets.

Initial U.S. Approval: 1976

WARNING: TARDIVE DYSKINESIA

- Metoclopramide Orally Disintegrating Tablets can cause tardive dyskinesia (TD), a serious movement disorder that is often irreversible. There is no known treatment for TD. The risk of developing TD increases with duration of treatment and total cumulative dosage. (5.1)
- Discontinue Metoclopramide Orally Disintegrating Tablets in patients who develop signs or symptoms of TD. (5.1)
- Avoid treatment with Metoclopramide Orally Disintegrating Tablets for longer than 12 weeks because of the risk of developing TD with longer-term use. (5.1, 2.1, 2.2, 2.3)

INDICATIONS AND USAGE

Metoclopramide Orally Disintegrating Tablets is a dopamine-2 (D2) antagonist indicated in adults for:
Treatment of symptomatic, documented gastroesophageal reflux disease (GERD) in adults with who fail to respond to conventional therapy.
Relief of symptoms associated with acute and recurrent diabetic gastroparesis (gastric stasis).
Limitations of Use:
Metoclopramide Orally Disintegrating Tablets is not recommended for use in pediatric patients due to the risk of developing tardive dyskinesia (TD) and other extrapyramidal symptoms and the risk of methemoglobinemia in neonates. (1, 8.4)

DOSAGE AND ADMINISTRATION

GERD
The recommended dosage is 10 mg to 15 mg up to four times daily at least 30 minutes before eating and at bedtime for 4 to 12 weeks. (2.2)
Diabetic Gastroparesis (Gastric Stasis)
The recommended dosage is 10 mg dose four times daily at least 30 minutes before eating and at bedtime for 2 to 8 weeks. (2.3)
Dosage Adjustment in Specific Populations

- See Full Prescribing Information for recommended dosage reductions for elderly patients, patients with moderate or severe hepatic or renal impairment, and cytochrome P450 2D6 (CYP2D6) poor metabolizers. (2.2, 2.3)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- History of TD or dystonic reaction to metoclopramide (4)
- When stimulation of gastrointestinal motility might be dangerous (4)
- Pheochromocytoma, catecholamine-releasing paragangliomas (4)
- Epilepsy (4)
- Hypersensitivity to metoclopramide (4)

WARNINGS AND PRECAUTIONS

- Tardive Dyskinesia (TD), Other Extrapyramidal Symptoms (EPS), and Neuroleptic Malignant Syndrome (NMS): Avoid concomitant use of other drugs known to cause TD/EPS/NMS and avoid use in patients with Parkinson's disease. If symptoms occur, discontinue Metoclopramide Orally Disintegrating Tablets and seek immediate medical attention. (5.1, 5.2, 5.3, 7.1, 7.2)
- Depression and suicidal ideation/suicide : Avoid use. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (> 10%) are restlessness, drowsiness, fatigue, and lassitude. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-866-403-7592 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

- Antipsychotics: Potential for additive effects, including TD, EPS, and NMS ; avoid concomitant use. (7.1)
- CNS depressants : Increased risk of CNS depression; avoid concomitant use and monitor for adverse reactions. (7.1)
- Strong CYP2D6 inhibitors (e.g., quinidine, bupropion, fluoxetine, and paroxetine) : See Full Prescribing Information for recommended dosage reductions. (2.2, 2.3, 7.1)
- MAO inhibitors : Increased risk of hypertension; avoid concomitant use. (5.5, 7.1)
- Additional drug interactions : See Full Prescribing Information. (7.1, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING TARDIVE DYSKINESIA

- Metoclopramide Orally Disintegrating Tablets can cause tardive dyskinesia (TD), a serious movement disorder that is often irreversible. There is no known treatment for TD. The risk of developing TD increases with duration of treatment and total cumulative dosage [see Warnings and Precautions (5.1)].
- Discontinue Metoclopramide Orally Disintegrating Tablets in patients who develop signs or symptoms of TD. In some patients, symptoms may lessen or resolve after Metoclopramide Orally Disintegrating Tablets is stopped [see Warnings and Precautions (5.1)].
- Avoid treatment with Metoclopramide Orally Disintegrating Tablets for longer than 12 weeks because of the increased risk of developing TD with longer-term use [see Warnings and Precautions (5.1), Dosage and Administration (2.2, 2.3)].

1 INDICATIONS AND USAGE

Metoclopramide Orally Disintegrating Tablets is indicated in adults for the:

- Treatment for 4 to 12 weeks of symptomatic, documented gastroesophageal reflux disease (GERD) who fail to respond to conventional therapy.
- Relief of symptoms associated with acute and recurrent diabetic gastroparesis (gastric stasis).

Limitations of Use:

Metoclopramide Orally Disintegrating Tablets is not recommended for use in pediatric patients due to the risk of developing tardive dyskinesia (TD) and other extrapyramidal symptoms and the risk of methemoglobinemia in neonates *[see Use in Specific Populations (8.4)]*

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Avoid treatment with Metoclopramide Orally Disintegrating Tablets for longer than 12 weeks because of the increased risk of developing TD with longer-term use [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)].
- Take on an empty stomach at least 30 minutes before eating [see Clinical Pharmacology (12.3)]. Do not repeat dose if inadvertently taken with food.
- 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.
- Place the tablet on the tongue and allow it to disintegrate (takes approximately one minute) and swallow the granules without water [see Clinical Pharmacology (12.3)].

2.2 Dosage for GERD

Metoclopramide Orally Disintegrating Tablets may be administered continuously or intermittently in patients with symptomatic GERD who fail to respond to conventional therapy:

Continuous Dosing

The recommended adult dosage of Metoclopramide Orally Disintegrating Tablets is 10 to 15 mg four times daily for 4 to 12 weeks. The treatment duration is determined by endoscopic response. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 60 mg.

Table 1 displays the recommended daily dosage and maximum daily dosage for adults and dosage adjustments for patients with moderate or severe hepatic impairment (Child-Pugh B or C), in patients with creatinine clearance less than 60 mL/minute, in cytochrome P450 2D6 (CYP2D6) poor metabolizers, and with concomitant use with strong CYP2D6 inhibitors.

Intermittent Dosing

If symptoms only occur intermittently or at specific times of the day, administer Metoclopramide Orally Disintegrating Tablets in single dose up to 20 mg prior to the provoking situation. Consider dosage reductions for the populations and situations in Table 1.

Table 1 Recommended Metoclopramide Orally Disintegrating Tablets Dosage in Patients with Gastroesophageal Reflux

<table>
<tr><th></th><th>Recommended Dosage</th><th>Maximum Recommended Daily Dosage</th></tr>
<tr><td>Adult patients</td><td rowspan="2">10 to 15 mg four times daily
(thirty minutes before each meal and at bedtime)</td><td rowspan="3">60 mg</td></tr>
<tr><td>Mild hepatic impairment (Child-Pugh A)</td></tr>
<tr><td>Elderly patients1
[see Use in Specific Populations (8.5)]</td><td>5 mg four times daily
(thirty minutes before each meal and at bedtime)</td></tr>
<tr><td>Moderate or severe hepatic impairment (Child-Pugh B or C)
[see Use in Specific Populations (8.7)]</td><td rowspan="5">5 mg four times daily
(thirty minutes before each meal and at bedtime), or
10 mg taken three times daily</td><td rowspan="5">30 mg</td></tr>
<tr><td>CYP2D6 poor metabolizers
[see Use in Specific Populations (8.9)]</td></tr>
<tr><td>Concomitant use with strong CYP2D6 inhibitors (e.g., quinidine, bupropion, fluoxetine, and paroxetine)
[see Drug Interactions (7.1)]</td></tr>
<tr><td>Moderate or severe renal impairment (creatinine clearance less than or equal to 60 mL/minute)
[see Use in Specific Populations (8.6)]</td></tr>
<tr><td>Patients with End-Stage Renal Disease (ESRD) including those treated with hemodialysis and continuous ambulatory peritoneal dialysis</td><td>5 mg four times daily
(thirty minutes before each meal and at bedtime) or
10 mg twice daily</td><td>20 mg</td></tr>
</table>

[see Use in Specific Populations (8.6)]		

[1]Elderly patients may be more sensitive to the therapeutic or adverse effects of Metoclopramide Orally Disintegrating Tablets; therefore, consider a lower starting dosage of 5 mg four times daily with titration to the recommended adult dosage of 10 to 15 mg four times daily based upon response and tolerability.

2.3 Dosage for Acute and Recurrent Diabetic Gastroparesis (Gastric Stasis)

The recommended adult dosage for the relief of symptoms associated with diabetic gastroparesis (gastric stasis) is 10 mg four times daily for 2 to 8 eight weeks, depending on symptomatic response. Avoid Metoclopramide Orally Disintegrating Tablets treatment for greater than 12 weeks *[see Warnings and Precautions (5.1)]* . Administer the dosage at least 30 minutes before each meal and at bedtime. The maximum recommended daily dosage is 40 mg.

Table 2 displays the recommended daily dosage and maximum daily dosage for adults and dosage adjustments for patients with moderate or severe hepatic impairment (Child-Pugh B or C), in patients with creatinine clearance less than 60 mL/minute, in cytochrome P450 2D6 (CYP2D6) poor metabolizers, and with concomitant use with strong CYP2D6 inhibitors.

If patients with diabetic gastroparesis have severe nausea or vomiting and are unable to take oral Metoclopramide Orally Disintegrating Tablets tablets, consider starting therapy with metoclopramide injection given intramuscularly or intravenously for up to 10 days (see the prescribing information for metoclopramide injection). After patients are able to take oral therapy, switch to Metoclopramide Orally Disintegrating Tablets tablets.

Table 2 Recommended Metoclopramide Orally Disintegrating Tablets Dosage in Patients with Acute and Recurrent Diabetic Gastroparesis

	Recommended Dosage	Maximum Recommended Daily Dosage
Adult patients	10 mg four times daily (thirty minutes before each meal and at bedtime)	40 mg
Mild hepatic impairment (Child-Pugh A)		
Elderly patients *[see Use in Specific Populations (8.5)]*	5 mg[1] four times daily (thirty minutes before each meal and at bedtime)	
Moderate or severe hepatic impairment (Child-Pugh B or C) *[see Use in Specific Populations (8.7)]*	5 mg four times daily (thirty minutes before each meal and at bedtime)	20 mg
CYP2D6 poor metabolizers *[see Use in Specific Populations (8.9)]*		
Concomitant use with strong CYP2D6 inhibitors (e.g., quinidine, bupropion, fluoxetine, and paroxetine) *[see Drug Interactions (7.1)]*		
Moderate or severe renal impairment (creatinine clearance less than or equal to 60 mL/minute) *[see Use in Specific Populations (8.6*		

)]		
Patients with End-Stage Renal Disease (ESRD) including those treated with hemodialysis and continuous ambulatory peritoneal dialysis *[see Use in Specific Populations (8.6)]*	5 mg twice daily	10 mg

[1]Elderly patients may be more sensitive to the therapeutic or adverse effects of Metoclopramide Orally Disintegrating Tablets; therefore, consider a lower dosage of 5 mg four times daily with titration to the recommended adult dosage of 10 mg four times daily based upon response and tolerability.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 5 mg Tablets: Metoclopramide Orally Disintegrating Tablets are round, white to off- white, flat faced beveled edge tablet, debossed with 'N' on one side and "581" on the other side.
- 10 mg Tablets: Metoclopramide Orally Disintegrating Tablets are round, white to off- white, flat faced beveled edge tablet, debossed with 'N' on one side and "580" on the other side.

4 CONTRAINDICATIONS

Metoclopramide Orally Disintegrating Tablets is contraindicated:

- In patients with a history of tardive dyskinesia (TD) or a dystonic reaction to metoclopramide [see Warnings and Precautions (5.1, 5.2)].
- When 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. Reglan may cause a hypertensive/pheochromocytoma crisis, probably due to release of catecholamines from the tumor [see Warnings and Precautions (5.5)].
- In patients with epilepsy. Reglan may increase the frequency and severity of seizures [see Adverse Reactions (6)].
- In patients with hypersensitivity to metoclopramide. Reactions have included laryngeal and glossal angioedema and bronchospasm [see Adverse Reactions (6)].

5 WARNINGS AND PRECAUTIONS

5.1 Tardive Dyskinesia

Metoclopramide can cause tardive dyskinesia (TD), a potentially irreversible and disfiguring disorder characterized by involuntary movements of the face or tongue, and sometimes of the trunk and/or extremities. Movements may be choreoathetoic in appearance. The risk of developing TD and the likelihood that TD will become irreversible increases with the duration of treatment and total cumulative dosage. An analysis of utilization patterns showed that about 20% of patients who used metoclopramide took it for longer than 12 weeks. Treatment with metoclopramide for longer than the recommended 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing TD.

Additionally, the risk of developing TD is increased among the elderly, especially elderly women *[see Use in Specific Populations (8.5)]* , and in patients with diabetes mellitus. Due to the risk of developing TD, avoid treatment with Metoclopramide Orally Disintegrating Tablets for longer than 12 weeks and reduce the dosage in elderly patients *[see Dosage and Administration (2.2, 2.3)]*.

Discontinue Metoclopramide Orally Disintegrating Tablets immediately in patients who develop signs and 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 Orally Disintegrating Tablets is withdrawn.

Metoclopramide Orally Disintegrating Tablets 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. Metoclopramide Orally Disintegrating Tablets is contraindicated in patients with a history of TD *[see Contraindications (4)]*. Avoid Metoclopramide Orally Disintegrating Tablets in patients receiving other drugs that can cause TD (e.g., antipsychotics).

5.2 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 Metoclopramide Orally Disintegrating Tablets.

- Extrapyramidal symptoms (EPS), such as acute dystonic reactions, occurred in patients treated with metoclopramide dosages of 30 to 40 mg daily. Such reactions occurred more frequently in adults less than 30 years of age and at higher than recommended dosages. EPS occurred more frequently in pediatric patients compared to adults (Metoclopramide Orally Disintegrating Tablets is not approved for use in pediatric patients). 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 Metoclopramide Orally Disintegrating Tablets in patients receiving other drugs that can cause EPS (e.g., antipsychotics).
- Parkinsonism 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 following discontinuation of metoclopramide. Avoid Metoclopramide Orally Disintegrating Tablets in patients with Parkinson's disease and other patients being treated with antiparkinsonian drugs due to potential exacerbation of symptoms. Avoid treatment with Metoclopramide Orally Disintegrating Tablets for more than 12 weeks [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)].
- 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.

5.3 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 Metoclopramide Orally Disintegrating Tablets in patients receiving other drugs associated with NMS, including typical and atypical antipsychotics.

Clinical manifestations of NMS include hyperthermia, 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 illness (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 Metoclopramide Orally Disintegrating Tablets and other drugs not essential to concurrent therapy [see Drug Interactions (7.1)].
- Intensive symptomatic treatment and medical monitoring.
- Treatment of any concomitant serious medical problems for which specific treatments are available.

5.4 Depression

Depression has occurred in metoclopramide-treated patients with and without a history of depression. Symptoms have included suicidal ideation and suicide. Avoid Metoclopramide Orally Disintegrating Tablets use in patients with a history of depression.

5.5 Hypertension

Metoclopramide may elevate blood pressure. In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, avoid use in patients with hypertension or in patients taking monoamine oxidase inhibitors *[see Drugs Interactions (7.1)]* .

There are also clinical reports of hypertensive crises in some patients with undiagnosed pheochromocytoma. Metoclopramide Orally Disintegrating Tablets is contraindicated in patients with pheochromocytoma or other catecholamine-releasing paragangliomas *[see Contraindications (4)]* . Discontinue Metoclopramide Orally Disintegrating Tablets in any patient with a rapid rise in blood pressure.

5.6 Fluid Retention

Because 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. Discontinue Metoclopramide Orally Disintegrating Tablets if any of these adverse reactions occur.

5.7 Hyperprolactinemia

As with other dopamine D2 antagonists, metoclopramide elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients.

Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, including metoclopramide.

Hyperprolactinemia may potentially stimulate prolactin-dependent breast cancer. However, some clinical studies and epidemiology studies have not shown an association between administration of dopamine D2 antagonists and tumorigenesis in humans *[see Nonclinical Toxicology (13.1)]*.

5.8 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 Metoclopramide Orally Disintegrating Tablets or the interacting drug, depending on the importance of the drug to the patient *[see Drug Interactions (7.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections of the labeling:

- Tardive dyskinesia [see Boxed Warning and Warnings and Precautions (5.1)]

- Other extrapyramidal effects [see Warnings and Precautions (5.2)]
- Neuroleptic malignant syndrome [see Warnings and Precautions (5.3)]
- Depression [see Warnings and Precautions (5.4)]
- Hypertension [see Warnings and Precautions (5.5)]
- Fluid retention [see Warnings and Precautions (5.6)]
- Hyperprolactinemia [see Warnings and Precautions (5.7)]
- Effects on the ability to drive and operate machinery [see Warnings and Precautions (5.8)]

Metoclopramide

The following adverse reactions have been identified from clinical studies or postmarketing reports of metoclopramide. Because these 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.

The most common adverse reactions (in approximately 10% of patients receiving 10 mg of metoclopramide four times daily) were restlessness, drowsiness, fatigue, and lassitude. In general, the incidence of adverse reactions correlated with the dosage and duration of metoclopramide administration.

Adverse reactions, especially those involving the nervous system, occurred after stopping metoclopramide including dizziness, nervousness, and headaches.

Central Nervous System Disorders

- Tardive dyskinesia, acute dystonic reactions, drug-induced parkinsonism, akathisia, and other extrapyramidal symptoms
- Convulsive seizures
- Hallucinations
- Restlessness, drowsiness, fatigue, and lassitude occurred in approximately 10% of patients who received 10 mg four times daily. Insomnia, headache, confusion, dizziness, or depression with suicidal ideation occurred less frequently
- Neuroleptic malignant syndrome, serotonin syndrome (in combination with serotonergic agents)

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

Cardiovascular Disorders: Acute congestive heart failure, possible atrioventricular block, hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention

Gastrointestinal Disorders: Nausea, bowel disturbances (primarily diarrhea)

Hepatic Disorders: Hepatotoxicity, characterized by, e.g., jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential

Renal and Urinary Disorders: Urinary frequency, urinary incontinence

Hematologic Disorders: Agranulocytosis, neutropenia, leukopenia, methemoglobinemia, sulfhemoglobinemia

Hypersensitivity Reactions: Bronchospasm (especially in patients with a history of asthma), urticaria; rash; angioedema, including glossal or laryngeal edema

Eye Disorders: Visual disturbances

Metabolism Disorders: Porphyria

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Metoclopramide

Table 3 displays the 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 *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.
Strong CYP2D6 Inhibitors, not Included in Antipsychotic Category Above	
Clinical Impact	Increased plasma concentrations of metoclopramide; risk of exacerbation of extrapyramidal symptoms *[see Clinical Pharmacology (12.3)]*.
Intervention	Reduce the Metoclopramide Orally Disintegrating Tablets dosage [*see Dosage and Administration (2.2 , 2.3)]* .
Examples	quinidine, bupropion, fluoxetine, and paroxetine.
Monoamine Oxidase Inhibitors	
Clinical Impact	Increased risk of hypertension *[see Warnings and Precautions (5.5)]*.
Intervention	Avoid concomitant use.
Central Nervous System (CNS) Depressants	
Clinical Impact	Increased risk of CNS depression *[see Warnings and Precautions (5.8)]*.
Intervention	Avoid Metoclopramide Orally Disintegrating Tablets 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, a D2 antagonist, due to opposing effects on dopamine.
Intervention	Monitor for reduced therapeutic effect.
Examples	Apomorphine, bromocriptine, cabergoline, levodopa, pramipexole, ropinirole, and rotigotine.

7.2 Effects of Metoclopramide on Other Drugs

Table 4 displays the effects of metoclopramide on other drugs.

Dopaminergic Agonists and Other Drugs that Increase 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 *[see Warnings and Precautions (5.2)]* .
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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published studies, including retrospective cohort studies, national registry studies, and meta-analyses, do not report an increased risk of adverse pregnancy-related outcomes with use of metoclopramide during pregnancy.

There are potential risks to the neonate following exposure in utero to metoclopramide during delivery *(see Clinical Considerations)*. In animal reproduction studies, no adverse developmental effects were observed with oral administration of metoclopramide to pregnant rats and rabbits at exposures about 6 and 12 times the maximum recommended human dose (MRHD) *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Metoclopramide crosses the placental barrier and may cause extrapyramidal signs and methemoglobinemia in neonates with maternal administration during delivery. Monitor neonates for extrapyramidal signs *[see Warnings and Precautions (5.1, 5.2), Use in Specific Populations (8.4)]* .

Data

Animal Data

Reproduction studies have been performed following administration of oral metoclopramide during organogenesis in pregnant rats at about 6 times the MRHD calculated on body surface area and in pregnant rabbits at about 12 times the MRHD calculated on body surface area. No evidence of adverse developmental effects due to metoclopramide were observed.

8.6 Lactation

Risk Summary

Limited published data report the presence of metoclopramide in human milk in variable amounts. Breastfed infants exposed to metoclopramide have experienced gastrointestinal adverse reactions, including intestinal discomfort and increased intestinal gas formation *(see Data)*. Metoclopramide elevates prolactin levels *[see Warnings and Precautions (5.7)]* ; however, the published data are not

adequate to support drug effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Metoclopramide Orally Disintegrating Tablets and any potential adverse effects on the breastfed child from Metoclopramide Orally Disintegrating Tablets or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding neonates because metoclopramide may cause extrapyramidal signs (dystonias) and methemoglobinemia *[see Warnings and Precautions (5.1, 5.2), Use in Specific Populations (8.4)]* .

Data

In published clinical studies, the estimated amount of metoclopramide received by the breastfed infant was less than 10% of the maternal weight-adjusted dose. In one study, the estimated daily amount of metoclopramide received by infants from breast milk ranged from 6 to 24 mcg/kg/day in early puerperium (3 to 9 days postpartum) and from 1 to 13 mcg/kg/day at 8 to 12 weeks postpartum.

8.4 Pediatric Use

Metoclopramide Orally Disintegrating Tablets is not recommended for use in pediatric patients due to the risk of tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates. The safety and effectiveness of Metoclopramide Orally Disintegrating Tablets in pediatric patients have not been established.

Dystonias and other extrapyramidal reactions associated with metoclopramide are more common in the pediatric patients than in adults *[see Warnings and Precautions (5.1, 5.2)]* . 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 *[see Use in Specific Populations (8.8)]* .

8.5 Geriatric Use

Metoclopramide is known to be substantially excreted by the kidney, and the risk of adverse reactions, including tardive dyskinesia (TD), may be greater in patients with impaired renal function *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]* . Elderly patients are more likely to have decreased renal function and may be more sensitive to the therapeutic or adverse effects of metoclopramide; therefore, consider a reduced dosage of METOZOLOV ODT in elderly patients *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)].*

8.7 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.

Reduce the Metoclopramide Orally Disintegrating Tablets dosage in patients with moderate and severe renal impairment (creatinine clearance less than or equal to 60 mL/minute), including those receiving hemodialysis and continuous ambulatory peritoneal dialysis *[see Dosage and Administration (2.2, 2.3), Clinical Pharmacology (12.3)].*

8.8 Hepatic Impairment

Patients with severe hepatic impairment (Child-Pugh C) have reduced systemic metoclopramide clearance (by approximately 50%) compared to patients with normal hepatic function. The resulting increase in metoclopramide blood concentrations increases the risk of adverse reactions. There are no pharmacokinetic data in patients with moderate hepatic impairment (Child-Pugh B). Reduce Metoclopramide Orally Disintegrating Tablets dosage in patients with moderate or severe (Child-Pugh B or C) hepatic impairment *[see Dosage and Administration (2.2 , 2.3)]* . There is no dosage adjustment required for patients with mild hepatic impairment (Child-Pugh A).

In addition, metoclopramide, by producing a transient increase in plasma aldosterone, may increase the risk of fluid retention in patients with hepatic impairment *[see Warnings and Precautions (5.6)]* .

Monitor patients with hepatic impairment for the occurrence of fluid retention and volume overload.

8.9 NADH-Cytochrome b5 Reductase Deficiency

Metoclopramide-treated patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia. For patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency the metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended. Methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal *[see Overdosage (10)]* .

8.10 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 Metoclopramide Orally Disintegrating Tablets *[see Clinical Pharmacology (12.3)]*. Reduce the Metoclopramide Orally Disintegrating Tablets dosage in patients who are poor CYP2D6 metabolizers *[see Dosage and Administration (2.2, 2.3)]*.

10 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 and Precautions (5.1, 5.2, 5.3)]*.

There are no specific antidotes for Metoclopramide Orally Disintegrating Tablets 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.

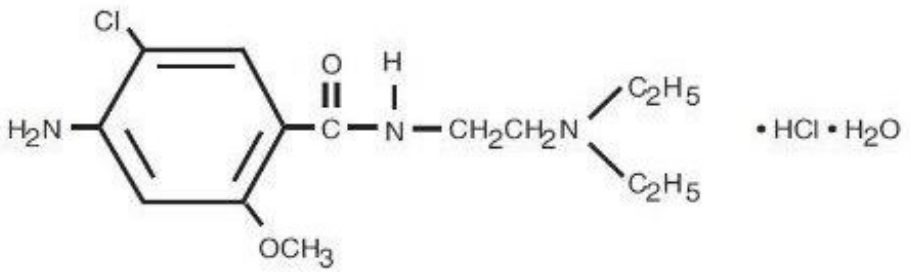
Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal.

11 DESCRIPTION

Metoclopramide hydrochloride, the active ingredient of Metoclopramide Orally Disintegrating Tablets, is a dopamine-2 (D2) antagonist.

Metoclopramide hydrochloride (metoclopramide monohydrochloride monohydrate), is a white or almost white crystalline powder, freely soluble in water. Chemically, it is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate.

The molecular formula is C14H22ClN3O2•HCl•H2O. Its molecular weight is 354.3. The structural formula is:



Metoclopramide Orally Disintegrating Tablets is an orally disintegrating tablet for oral administration and is available in 5 mg and 10 mg strengths.

- Each Metoclopramide Orally Disintegrating Tablets 5 mg tablet contains 5 mg metoclopramide (equivalent to 5.91 mg of metoclopramide hydrochloride USP).
- Each Metoclopramide Orally Disintegrating Tablets 10 mg tablet contains 10 mg metoclopramide (equivalent to 11.82 mg metoclopramide hydrochloride USP).
- Metoclopramide Orally Disintegrating Tablets includes the following inactive ingredients: phosphoric acid, mannitol and starch, microcrystalline cellulose, colloidal silicon dioxide, amino methacrylate copolymer, butylated hydroxyanisole, butylated hydroxytoluene, crospovidone, aspartame, N-C mint flavor, magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. The exact mechanism of action of metoclopramide in the treatment of gastroesophageal reflux and acute and recurrent diabetic gastroparesis has not been fully established. 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.

12.2 Pharmacodynamics

Gastroesophageal Reflux

In patients with gastroesophageal reflux and low lower esophageal sphincter pressure (LESP), single oral doses of Reglan produced dose-related increases in LESP. Effects began at about 5 mg and increased through 20 mg. The increase in LESP from a 5 mg dose lasted about 45 minutes and that of 20 mg lasted between 2 and 3 hours. Increased rate of stomach emptying was observed with single oral doses of 10 mg.

12.3 Pharmacokinetics

Unless otherwise specified the PK of metoclopramide described below was obtained using other oral formulations of metoclopramide.

Absorption

Relative to an intravenous dose of 20 mg, the absolute oral bioavailability of metoclopramide was 80% ± 15.5% as demonstrated in a crossover study of 18 subjects.

Following Metoclopramide Orally Disintegrating Tablets tablet administration, the 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 two clinical trials (N = 96) with a mean ± SD being 77 ± 111 seconds and a median of 54 seconds *[see Dosage and Administration (2.1)]* .

Peak plasma concentrations occurred at about 1 to 2 hours 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 showed that the area under the drug concentration-time curve increases linearly with doses from 20 to 100 mg of metoclopramide (5 times the maximum recommended single dose of Metoclopramide Orally Disintegrating Tablets).

Cmax increased linearly with dose; Tmax remained the same; whole body clearance was unchanged; and the elimination rate remained the same. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

The pharmacokinetic characteristics following single oral administration of 10 mg Metoclopramide Hydrochloride Orally Disintegrating Tablets under fasting conditions are shown in Table 5.

Table 5 Mean (± SD) Pharmacokinetic Parameters in Healthy Subjects Following a Single Oral Dose of 10 mg Metoclopramide Orally Disintegrating Tablets Under Fasting Conditions

Treatment	**C_{max} (ng/mL)**	**T_{max}(h)***	**$AUC_{0\text{-}inf}$ (ng*h/mL)**
Single 10 mg Metoclopramide Orally Disintegrating Tablets (N=41)	28±7.4	2.0 (0.7 to 4.0)	268±72.6

*presented as median (range).

Effect of Food

When Metoclopramide Orally Disintegrating Tablets was taken immediately after a high-fat meal (approximately 900 total calories based on the composition being 150 protein calories, 250 carbohydrate calories and 500 fat calories), the Cmax was 17% lower than when taken after an overnight fast. The Tmax increased from about 1.8 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 Metoclopramide Orally Disintegrating Tablets was administered with or without food. The clinical relevance of a lower Cmax with a high-fat meal is unknown *[see Dosage and Administration (2.1)]* .

Distribution

Metoclopramide 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.

Elimination

The average elimination half-life of metoclopramide in subjects with normal renal function was 5 to 6 hours

Metabolism

Metoclopramide undergoes enzymatic metabolism via oxidation as well as glucuronide and sulfate conjugation reactions in the liver. Monodeethylmetoclopramide, a major oxidative metabolite, is formed primarily by CYP2D6, an enzyme subject to genetic variability *[see Dosage and Administration (2.2, 2.3), Use in Specific Populations (8.9)]* .

Excretion

Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hours. After oral administration of 10 or 20 mg, a mean of 18% and 22% of the dose, respectively, was recovered as free metoclopramide in urine within 36 hours.

Specific Populations

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 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 on dialysis was about 3.5-fold the AUC in subjects with normal renal function *[see Dosage and Administration (2.2, 2.3), Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

In a group of 8 patients with severe hepatic impairment (Child-Pugh C), the average metoclopramide clearance was reduced by approximately 50% compared to patients with normal hepatic function *[see Dosage and Administration (2.2, 2.3), Use in Specific Populations (8.7)]*.

Drug Interaction Studies

Effect of Metoclopramide on CYP2D6 Substrates

Although in vitro studies suggest that metoclopramide can inhibit CYP2D6, metoclopramide is unlikely to interact with CYP2D6 substrates *in vivo* at therapeutically relevant concentrations.

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 Cmax and AUC0-∞, respectively, compared to patients who received metoclopramide alone (see Table 6 Metoclopramide Pharmacokinetic Parameters in Healthy Subjects with and without Fluoxetine) *[see Drug Interactions (7.1)]* .

Table 6 Metoclopramide Pharmacokinetic Parameters in Healthy Subjects with and without Fluoxetine

Parameter	**Metoclopramide alone (mean ± SD)**	**Metoclopramide with fluoxetine (mean ± SD)**
Cmax (ng/mL)	44 ±15	62.7 ± 9.2
AUC0-∞ (ng□h/mL)	313 ± 113	591 ± 140
t1/2 (h)	5.5 ± 1.1	8.5 ± 2.2

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A 77-week study was conducted in rats with oral metoclopramide doses up to 40 mg/kg/day (about six times the maximum recommended human dose on body surface area basis). Metoclopramide elevated prolactin levels and the elevation persisted during chronic administration. An increase in mammary neoplasms was found in rodents after chronic administration of metoclopramide *[see Warnings and Precautions (5.7)]*. In a rat model for assessing the tumor promotion potential, a 2-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.

Mutagenesis

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 assay with rat and human hepatocytes and the *in vivo* rat micronucleus assay.

Impairment of Fertility

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

Metoclopramide Orally Disintegrating Tablets 5 mg strength are round, white to off- white, flat faced beveled edge tablet debossed with 'N' on one side and "581" on the other side; it is comprised of 5 mg metoclopramide (as 5.91 mg of metoclopramide hydrochloride). These are packaged in blister cards as follows:

Box of 10 (1x10) NDC 43386-581-31

Metoclopramide Orally Disintegrating Tablets 10 mg are round, white to off-white, flat faced beveled edge tablet debossed with 'N' on one side and "580" on the other side; it is comprised of 10 mg metoclopramide (as 11.82 mg of metoclopramide hydrochloride). These are packaged in blister cards as follows:

Box of 10 (1x10) NDC 43386-580-31

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Adverse Reactions

Inform patients or their caregivers that Metoclopramide Orally Disintegrating Tablets can cause serious adverse reactions. Instruct patients to discontinue Metoclopramide Orally Disintegrating Tablets and contact a healthcare provider immediately if the following serious reactions occur:

- Tardive dyskinesia and other extrapyramidal reactions [see Warnings and Precautions (5.1, 5.2)]
- Neuroleptic malignant syndrome [see Warnings and Precautions (5.3)]
- Depression and/or possible suicidal ideation [see Warnings and Precautions (5.4)]

Inform patients or their caregivers that 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 *[see Drug Interactions (7.1, 7.2)]* . Explain that the prescriber of any other medication must be made aware that the patient is taking Metoclopramide Orally Disintegrating Tablets.

Inform patients or their caregivers that Metoclopramide Orally Disintegrating Tablets 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 *[see Warnings and Precautions (5.8)]* .

Administration

Instruct patients to:

- Take on an empty stomach at least 30 minutes before eating. Do not repeat dose if inadvertently taken with food.
- 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.

- Place the tablet on the tongue and allow it to disintegrate (takes approximately one minute) and swallow the granules without water [see Dosage and Administration (2.1)].

Manufactured by:

Novel Laboratories, Inc.

Somerset, NJ 08873 USA

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, MD 21202

PI5800000203

SAP code: 260278

Rev. 10/2019

SPL MEDGUIDE

Metoclopramide Orally Disintegrating Tablets

(MET-oh-KLOE-pra-mide)

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

What is the most important information I should know about Metoclopramide Orally Disintegrating Tablets? Metoclopramide Orally Disintegrating Tablets can cause serious side effects, including:

Tardive dyskinesia (abnormal muscle movements). These movements happen mostly in the face muscles. You cannot control these movements. They may not go away even after stopping Metoclopramide Orally Disintegrating Tablets. There is no treatment for tardive dyskinesia, but symptoms may lessen or go away over time after you stop taking Metoclopramide Orally Disintegrating Tablets.

Your chances for getting tardive dyskinesia go up:

- the longer you take Metoclopramide Orally Disintegrating Tablets and the more Metoclopramide Orally Disintegrating Tablets you take. You should not take Metoclopramide Orally Disintegrating Tablets 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 tardive dyskinesia if you take Metoclopramide Orally Disintegrating Tablets. Call your doctor right away if you have movements you cannot 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 Metoclopramide Orally Disintegrating Tablets?" for more information about side effects.

What is Metoclopramide Orally Disintegrating Tablets?

Metoclopramide Orally Disintegrating Tablets 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.

Metoclopramide Orally Disintegrating Tablets is not recommended for use in children.

Do not take Metoclopramide Orally Disintegrating Tablets if you:

- have a history of tardive dyskinesia or have a problem controlling your muscles and movements after taking Metoclopramide Orally Disintegrating Tablets or a medicine that works like Metoclopramide Orally Disintegrating Tablets.
- have stomach or intestine problems that could get worse with Metoclopramide Orally Disintegrating Tablets, such as bleeding, blockage or a tear in your stomach or bowel wall.
- have a type of tumor that can cause high blood pressure such as pheochromocytoma.
- have epilepsy (seizures). Metoclopramide Orally Disintegrating Tablets can increase your chance for seizures and make them worse.
- are allergic to metoclopramide or any of the ingredients in Metoclopramide Orally Disintegrating Tablets. Metoclopramide Orally Disintegrating Tablets can cause serious allergic reactions. Stop taking Metoclopramide Orally Disintegrating Tablets right away and get emergency help if you have any of these symptoms:

- swelling of your tongue, throat, lips, eyes or face.
- trouble swallowing or breathing.
- skin rash, hives, sores in your mouth, or skin blisters.

See the end of this Medication Guide for a list of ingredients in Metoclopramide Orally Disintegrating Tablets.

Before you take Metoclopramide Orally Disintegrating Tablets, tell your doctor about all of your medical conditions, including if you:

- have kidney or liver disease.
- had problems controlling your muscle movements after taking any medicine.
- 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 breast cancer.
- drink alcohol.
- have seizures.
- are pregnant or plan to become pregnant. Metoclopramide Orally Disintegrating Tablets may harm your unborn baby if taken during the end of pregnancy. Talk to your healthcare provider if you become pregnant while taking Metoclopramide Orally Disintegrating Tablets.
- are breastfeeding or plan to breastfeed. Metoclopramide Orally Disintegrating Tablets can pass into your breastmilk and may harm your baby. You and your doctor should decide if you will take Metoclopramide Orally Disintegrating Tablets or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-countermedicines, vitamins, and herbal supplements. Metoclopramide Orally Disintegrating

Tablets 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 Metoclopramide Orally Disintegrating Tablets until you talk with your doctor.

Especially tell your doctor if you take:

- another medicine that contains metoclopramide, such as REGLAN injection, 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, used to treat mental illness such as schizophrenia
- 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 your medicines to show your doctor and pharmacist when you get new medicine.

How should I take Metoclopramide Orally Disintegrating Tablets?

- Take Metoclopramide Orally Disintegrating Tablets exactly as your doctor tells you. Do not change your dose unless your doctor tells you to.
- Take Metoclopramide Orally Disintegrating Tablets on an empty stomach at least 30 minutes before eating and at bedtime. Do not repeat your dose if you accidentally take it with food.
- Metoclopramide Orally Disintegrating Tablets comes as a tablet that melts in your mouth.
- Leave the tablet in the sealed blister Metoclopramide Orally Disintegrating Tablets pack until you are ready to take it.
- 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.
- Put the tablet on your tongue right away. Let it melt and then swallow. This should take about 1 minute. You do not need water to take Metoclopramide Orally Disintegrating Tablets.
- You should not take Metoclopramide Orally Disintegrating Tablets for more than 12 weeks.
- If you take too much Metoclopramide Orally Disintegrating Tablets, call your poison control center at 1-800-222-1222 or go to the nearest emergency room right away.

What should I avoid while taking Metoclopramide Orally Disintegrating Tablets?

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

What are the possible side effects of Metoclopramide Orally Disintegrating Tablets?

Metoclopramide Orally Disintegrating Tablets can cause serious side effects, including:

- **Tardive dyskinesia (abnormal muscle movements). See "What is the most important information I should know about Metoclopramide Orally Disintegrating Tablets?"**
- **Other changes in muscle control and movement, such as:**

- **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, and speech problems. These spasms usually start within the first 2 days of treatment. Rarely, these muscle spasms may cause trouble breathing. These spasms happen more often in adults younger than 30 years of age.
- **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

Metoclopramide Orally Disintegrating Tablets.

- **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 feet.

- **Neuroleptic Malignant Syndrome (NMS).** NMS is a rare but very serious condition that can happen with Metoclopramide Orally Disintegrating Tablets. 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 Metoclopramide Orally Disintegrating Tablets 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).
- **High blood pressure** . Metoclopramide Orally Disintegrating Tablets can cause your blood pressure to increase.
- **Too much body water** . People who have certain liver problems or heart failure and take Metoclopramide Orally Disintegrating Tablets 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.
- **Increased prolactin** . Tell your doctor if your menstrual periods stop, your breasts get larger and make milk, or you cannot have sex (impotence). These symptoms go away when you stop taking Metoclopramide Orally Disintegrating Tablets.

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 Metoclopramide Orally Disintegrating Tablets are:

- **restlessness**
- **drowsiness**
- **tiredness**
- **lack of energy**

You may have more side effects the longer you take Metoclopramide Orally Disintegrating Tablets and the more Metoclopramide Orally Disintegrating Tablets you take. You may still have side effects after stopping Metoclopramide Orally Disintegrating Tablets. You may have symptoms from stopping Metoclopramide Orally Disintegrating Tablets such as headaches and feeling dizzy or nervous.

Tell your doctor about any side effects that bothers you or that does not go away. These are not all the possible side effects of Metoclopramide Orally Disintegrating Tablets. 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 Metoclopramide Orally Disintegrating Tablets?

- Store Metoclopramide Orally Disintegrating Tablets at room temperature between 68° to 77°F (20° to 25°C).
- Keep Metoclopramide Orally Disintegrating Tablets away from moisture.
- Throw away any Metoclopramide Orally Disintegrating Tablets that is not used.

Keep Metoclopramide Orally Disintegrating Tablets and all medicines out of reach of children.

General information about the safe and effective use of Metoclopramide Orally Disintegrating

Tablets.

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

If you would like more information about Metoclopramide Orally Disintegrating Tablets, talk with your doctor. You can ask your doctor or pharmacist for information about Metoclopramide Orally Disintegrating Tablets that is written for health professionals. For more information, call 1-866-403-7592.

What are the ingredients in Metoclopramide Orally Disintegrating Tablets?

Active ingredient: Metoclopramide Hydrochloride, USP

Inactive ingredients: phosphoric acid, mannitol and starch, microcrystalline cellulose, colloidal silicon dioxide, amino methacrylate copolymer, butylated hydroxyanisole, butylated hydroxytoluene, crospovidone, aspartame, N-C mint flavor, magnesium stearate

Manufactured by:

Novel Laboratories, Inc.

Somerset, NJ 08873 USA

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, MD 21202

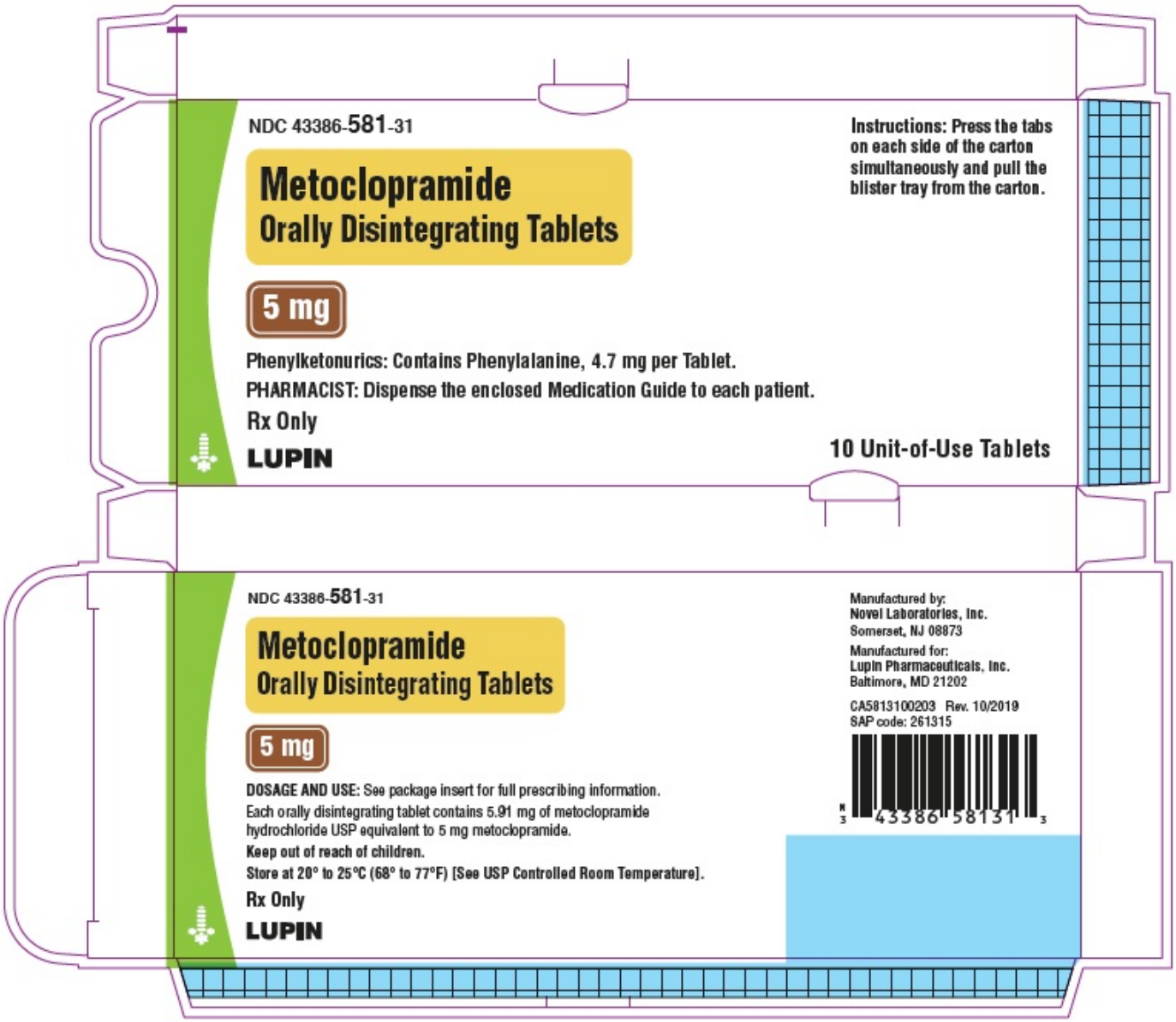
PI5800000203

SAP code: 260278

Rev. 10/2019

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: October 2019

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



NDC 43386-581-31

Metoclopramide
Orally Disintegrating Tablets

5 mg

Phenylketonurics: Contains Phenylalanine, 4.7 mg per Tablet.

PHARMACIST: Dispense the enclosed Medication Guide to each patient.

Rx Only

LUPIN

Instructions: Press the tabs on each side of the carton simultaneously and pull the blister tray from the carton.

10 Unit-of-Use Tablets

NDC 43386-581-31

Metoclopramide
Orally Disintegrating Tablets

5 mg

DOSAGE AND USE: See package insert for full prescribing information.

Each orally disintegrating tablet contains 5.91 mg of metoclopramide hydrochloride USP equivalent to 5 mg metoclopramide.

Keep out of reach of children.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Rx Only

LUPIN

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Lupin Pharmaceuticals, Inc.
Baltimore, MD 21202

CA5813100203 Rev. 10/2019
SAP code: 261315

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METOCLOPRAMIDE HYDROCHLORIDE

metoclopramide hydrochloride tablet, orally disintegrating

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43386-580
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METOCLOPRAMIDE HYDROCHLORIDE (UNII: W1792A2RVD) (METOCLOPRAMIDE - UNII:L4YEB44I46)	METOCLOPRAMIDE	10 mg

Inactive Ingredients	
Ingredient Name	**Strength**

PHOSPHORIC ACID (UNII: E4GA8884NN)	
MANNITOL (UNII: 3OWL53L36A)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	
CROSPOVIDONE (UNII: 2S7830E561)	
ASPARTAME (UNII: Z0H242BBR1)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	
DIMETHYLAMINOETHYL METHACRYLATE - BUTYL METHACRYLATE - METHYL METHACRYLATE COPOLYMER (UNII: 905HNO1SIH)	

Product Characteristics

Color	white (off-white)	**Score**	no score
Shape	ROUND	**Size**	12mm
Flavor		**Imprint Code**	N;580
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43386-580-31	1 in 1 CARTON	04/06/2015	
1		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202191	04/06/2015	

METOCLOPRAMIDE HYDROCHLORIDE

metoclopramide hydrochloride tablet, orally disintegrating

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43386-581
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METOCLOPRAMIDE HYDROCHLORIDE (UNII: W1792A2RVD) (METOCLOPRAMIDE - UNII:L4YEB44I46)	METOCLOPRAMIDE	5 mg

Inactive Ingredients

Ingredient Name	Strength
PHOSPHORIC ACID (UNII: E4GA8884NN)	
MANNITOL (UNII: 3OWL53L36A)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	
CROSPOVIDONE (UNII: 2S7830E561)	
ASPARTAME (UNII: Z0H242BBR1)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	
DIMETHYLAMINOETHYL METHACRYLATE - BUTYL METHACRYLATE - METHYL METHACRYLATE COPOLYMER (UNII: 905HNO1SIH)	

Product Characteristics

Color	white (off-white)	**Score**	no score
Shape	ROUND	**Size**	12mm
Flavor		**Imprint Code**	N;581
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43386-581-31	1 in 1 CARTON	04/06/2015	
1		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202191	04/06/2015	

Labeler - Lupin Pharmaceuticals,Inc. (089153071)

Registrant - Novel Laboratories, Inc. (793518643)

Establishment

Name	Address	ID/FEI	Business Operations
Novel Laboratories, Inc.		793518643	analysis(43386-580, 43386-581) , manufacture(43386-580, 43386-581) , pack(43386-580, 43386-581)

Revised: 12/2020 Lupin Pharmaceuticals,Inc.