

# METOCLOPRAMIDE HYDROCHLORIDE- metoclopramide hydrochloride tablet NuCare Pharmaceuticals, Inc.

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use METOCLOPRAMIDE TABLETS, USP safely and effectively. See full prescribing information for METOCLOPRAMIDE TABLETS, USP.

**METOCLOPRAMIDE tablets, USP, for oral use**

**Initial U.S. Approval: 1979**

### **WARNING: TARDIVE DYSKINESIA**

*See full prescribing information for complete boxed warning.*

- **Metoclopramide 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 tablets in patients who develop signs or symptoms of TD ( 5.1)**
- **Avoid treatment with metoclopramide 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)**

### **RECENT MAJOR CHANGES**

Boxed Warning	8/2017
Indications and Usage ( 1)	8/2017
Dosage and Administration, Dosage for Gastroesophageal Reflux ( 2.2)	8/2017
Dosage and Administration, Dosage for Acute and Recurrent Diabetic Gastroparesis ( 2.3)	8/2017
Contraindications ( 4)	8/2017
Warnings and Precautions, Tardive Dyskinesia ( 5.1)	8/2017
Warnings and Precautions, Other Extrapyrarnidal Symptoms ( 5.2)	8/2017
Warnings and Precautions, Neuroleptic Malignant Syndrome ( 5.3)	8/2017
Warnings and Precautions, Hyperprolactinemia ( 5.7)	8/2017

### **INDICATIONS AND USAGE**

Metoclopramide tablets, USP are indicated for the:

- Treatment for 4 to 12 weeks of symptomatic, documented gastroesophageal reflux in adults who fail to respond to conventional therapy. ( 1)
- Relief of symptoms in adults with acute and recurrent diabetic gastroparesis. ( 1)

#### Limitations of Use:

Metoclopramide tablets, USP are 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. ( 1, 8.4)

### **DOSAGE AND ADMINISTRATION**

#### Gastroesophageal Reflux ( 2.2)

- Administer metoclopramide tablets continuously or intermittently:
  - Continuous: Administer 10 to 15 mg, 30 minutes before each meal and at bedtime (maximum of 60 mg per day) for 4 to 12 weeks.
  - Intermittent: Single doses up to 20 mg prior to provoking situation.

#### Acute and Recurrent Diabetic Gastroparesis ( 2.3)

- Administer 10 mg, 30 minutes before each meal and at bedtime (maximum of 40 mg per day) for 2 to 8 weeks

Dosage Adjustment in Specific Populations ( 2.2, 2.3)

- For gastroesophageal reflux and acute and recurrent diabetic gastroparesis, see Full Prescribing Information for recommended dosage reductions for elderly patients, in patients with moderate or severe hepatic or renal impairment, and cytochrome P450 2D6 (CYP2D6) poor metabolizers.

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

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 Extrapyrarnidal 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 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 (greater than 10%) are restlessness, drowsiness, fatigue, and lassitude. ( 6)

**To report SUSPECTED ADVERSE REACTIONS, contact Impax Laboratories, Inc., at 1-800-934-6729 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

----- **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: 10/2017**

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## **FULL PRESCRIBING INFORMATION**

## BOXED WARNING

### WARNING: TARDIVE DYSKINESIA

- **Metoclopramide 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 tablets in patients who develop signs or symptoms of TD. In some patients, symptoms may lessen or resolve after metoclopramide tablets are stopped [see Warnings and Precautions (5.1)].**
- **Avoid treatment with metoclopramide tablets for longer than 12 weeks because of the increased risk of developing TD with longer-term use [see Warnings and Precautions (5.1) and Dosage and Administration (2.2, 2.3)]**

## 1 INDICATIONS AND USAGE

Metoclopramide tablets, USP are indicated for the: Metoclopramide tablets, USP are indicated for the:

- Treatment for 4 to 12 weeks of symptomatic, documented gastroesophageal reflux in adults who fail to respond to conventional therapy. Treatment for 4 to 12 weeks of symptomatic, documented gastroesophageal reflux in adults who fail to respond to conventional therapy.
- Relief of symptoms in adults with acute and recurrent diabetic gastroparesis. Relief of symptoms in adults with acute and recurrent diabetic gastroparesis.

Limitations of Use:

Metoclopramide tablets, USP are not recommended for use in pediatric patients due to the risk of developing tardive dyskinesia (TD) and other extrapyramidal symptoms as well as 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 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)].

### 2.2 Dosage for Gastroesophageal Reflux

Metoclopramide tablets may be administered continuously or intermittently in patients with symptomatic gastroesophageal reflux who fail to respond to conventional therapy: Metoclopramide tablets may be administered continuously or intermittently in patients

with symptomatic gastroesophageal reflux who fail to respond to conventional therapy:

### Continuous Dosing

The recommended adult dosage of metoclopramide 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. The recommended adult dosage of metoclopramide 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 tablets in single dose up to 20 mg prior to the provoking situation. Consider dosage reductions for the populations and situations in Table 1. If symptoms only occur intermittently or at specific times of the day, administer metoclopramide 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 Tablet Dosage in Patients with Gastroesophageal Reflux**

	<b>Recommended Dosage</b>	<b>Maximum Recommended Daily Dosage</b>
Adult patients Adult patients	10 to 15 mg four times daily (thirty minutes before each meal and at bedtime)	60 mg
Mild hepatic impairment (Child-Pugh A) Mild hepatic impairment (Child-Pugh A)	10 to 15 mg four times daily (thirty minutes before each meal and at bedtime)	
Elderly patients Elderly patients [see Use in Specific Populations (8.5)]	5 mg four times daily (thirty minutes before each meal and at bedtime) 5 mg *four times daily (thirty minutes before each meal and at bedtime)	
Moderate or severe hepatic impairment (Child-Pugh B or C) Moderate or		

severe hepatic impairment (Child-Pugh B or C) [see Use in Specific Populations (8.7)]		
CYP2D6 poor metabolizers CYP2D6 poor metabolizers [see Use in Specific Populations (8.9)]	5 mg four times daily (thirty minutes before each meal and at bedtime), or 10 mg taken three times daily	
Concomitant use with strong CYP2D6 inhibitors (e.g., quinidine, bupropion, fluoxetine, and paroxetine) Concomitant use with strong CYP2D6 inhibitors (e.g., quinidine, bupropion, fluoxetine, and paroxetine) [see Drug Interactions (7.1)]	5 mg four times daily (thirty minutes before each meal and at bedtime), or 10 mg taken three times daily	30 mg
Moderate or severe renal impairment (creatinine clearance less than or equal to 60 mL/minute) 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 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 four times daily (thirty minutes before each meal and at bedtime) or 10 mg twice daily 5 mg four times daily (thirty minutes before each meal and at bedtime) or 10 mg twice daily	20 mg

\* Elderly patients may be more sensitive to the therapeutic or adverse effects of metoclopramide 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

The recommended adult dosage for the treatment of acute and recurrent diabetic gastroparesis is 10 mg four times daily for 2 to 8 weeks, depending on symptomatic response. Avoid metoclopramide tablet treatment for greater than 12 weeks. Administer the dosage thirty minutes before each meal and at bedtime. The maximum recommended daily dosage is 40 mg. The recommended adult dosage for the treatment of acute and recurrent diabetic gastroparesis is 10 mg four times daily for 2 to 8 weeks, depending on symptomatic response. Avoid metoclopramide tablet treatment for greater than 12 weeks [see *Warnings and Precautions (5.1)*]. Administer the dosage thirty 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 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 tablets. If patients with diabetic gastroparesis have severe nausea or vomiting and are unable to take oral metoclopramide 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 tablets.

**Table 2. Recommended Metoclopramide Tablet Dosage in Patients with Acute and Recurrent Diabetic Gastroparesis**

	<b>Recommended Dosage</b>	<b>Maximum Recommended Daily Dosage</b>
Adult Patients	10 mg four times daily (30 minutes before each meal and at bedtime)	40 mg
Mild hepatic impairment (Child-Pugh A)	10 mg four times daily (30 minutes before each meal and at bedtime)	
Elderly patients [see <i>Use in Specific Populations (8.5)</i> ]	5 mg four times daily (30 minutes before each meal and at bedtime)	
Moderate or severe hepatic impairment (Child-Pugh B or C)		

impairment (Child-Pugh B or C) [see Use in Specific Populations (8.7)]		
CYP2D6 poor metabolizers CYP2D6 poor metabolizers [see Use in Specific Populations (8.9)]	5 mg four times daily (30 minutes before each meal and at bedtime) 5 mg four times daily (30 minutes before each meal and at bedtime)	20 mg
Concomitant use with strong CYP2D6 inhibitors (e.g., quinidine, bupropion, fluoxetine, and paroxetine) 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 60 mL/minute) Moderate or severe renal impairment (creatinine clearance less than 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 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 5 mg twice daily	10 mg

\* Elderly patients may be more sensitive to the therapeutic or adverse effects of metoclopramide 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 metoclopramide: Light green, round, unscored tablets, debossed **WPI** on one side and **2228** on the other side.
- 10 mg metoclopramide: White, round, scored tablets, debossed **WPI** on one side and **2229** on the other side.

### 4 CONTRAINDICATIONS

Metoclopramide tablets are contraindicated: Metoclopramide tablets are 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). 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. Metoclopramide tablets may cause a hypertensive/pheochromocytoma crisis, probably due to release of catecholamines from the tumor. In patients with pheochromocytoma or other catecholamine-releasing paragangliomas. Metoclopramide tablets 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. Metoclopramide tablets may increase the frequency and severity of seizures. In patients with epilepsy. Metoclopramide tablets 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. 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 syndrome of potentially irreversible and disfiguring involuntary movements of the face or tongue, and sometimes of the trunk and/or extremities. Movements may be choreoathetotic in appearance. The risk of developing TD and the likelihood that TD will become irreversible increases with duration of treatment and total cumulative dosage. Additionally, the risk of developing TD is increased among the elderly, especially elderly women, and in patients with diabetes mellitus. Due to the risk of developing TD, avoid treatment with metoclopramide tablets for longer than 12 weeks and reduce the dosage in elderly patients. Metoclopramide can cause tardive dyskinesia (TD), a syndrome of potentially irreversible and disfiguring involuntary movements of the face or tongue, and sometimes of the trunk and/or extremities. Movements may be choreoathetotic in appearance. The risk of developing TD and the likelihood that TD will become irreversible increases with duration of treatment and total cumulative dosage. Additionally, the risk of developing TD is increased 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 tablets for longer than 12 weeks and reduce the dosage in elderly patients [see *Dosage and Administration (2.2, 2.3)*].

Discontinue metoclopramide 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 tablets are withdrawn. Discontinue metoclopramide 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 tablets are 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. Metoclopramide tablets are contraindicated in patients with a history of TD. 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. Metoclopramide tablets are contraindicated in patients with a history of TD [see *Contraindications (4)*]. Avoid metoclopramide tablets in patients receiving other drugs that are likely to 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 tablets. 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 tablets.

- Extrapyramidal symptoms (EPS), such as acute dystonic reactions, occurred in patients treated with metoclopramide dosages of 30 mg to 40 mg daily. Such reactions occurred more frequently in adults less than 30 years of age and at higher than recommended dosages. EPS occurred more frequently in pediatric patients compared to adults (metoclopramide tablets are 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. Extrapyramidal symptoms (EPS), such as acute dystonic reactions, occurred in patients treated with metoclopramide dosages of 30 mg to 40 mg daily. Such reactions occurred more frequently in adults less than 30 years of age and at higher than recommended dosages. EPS occurred more frequently in pediatric patients compared to adults (metoclopramide tablets are 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 tablets in patients receiving other drugs that can cause EPS (e.g., antipsychotics).
- Parkinsonian symptoms (bradykinesia, tremor, cogwheel rigidity, mask-like facies) have occurred after starting metoclopramide, more commonly within the first 6 months, but also after longer periods. Symptoms generally have subsided within 2 to 3 months after discontinuation of metoclopramide tablets. Avoid treatment with metoclopramide tablets for more than 12 weeks . Parkinsonian symptoms (bradykinesia, tremor, cogwheel rigidity, mask-like facies) have occurred after starting metoclopramide, more commonly within the first 6 months, but also after longer periods. Symptoms generally have subsided within 2 to 3 months after discontinuation of metoclopramide tablets. Avoid metoclopramide 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 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. 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). Avoid metoclopramide tablets in patients receiving other drugs associated with NMS, including typical and atypical antipsychotics. 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 tablets in patients receiving other drugs associated with NMS, including typical and atypical antipsychotics.

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

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

Management of NMS includes: Management of NMS includes:

- Immediate discontinuation of metoclopramide tablets and other drugs not essential to concurrent therapy . Immediate discontinuation of metoclopramide tablets and other drugs not essential to concurrent therapy [*see Drug Interactions (7.1)*] .
- Intensive symptomatic treatment and medical monitoring. Intensive symptomatic treatment and medical monitoring.
- Treatment of any concomitant serious medical problems for which specific treatments are available. 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 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 *Drug Interactions (7.1)*].

There are also clinical reports of hypertensive crises in patients with undiagnosed pheochromocytoma. Metoclopramide tablets are contraindicated in patients with pheochromocytoma or other catecholamine-releasing paragangliomas [see *Contraindications (4)*]. Discontinue metoclopramide 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 tablets if any of these adverse reactions occur.

## 5.7 Hyperprolactinemia

As with other dopamine D<sub>2</sub> receptor 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 D<sub>2</sub> receptor 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 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)]

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.

**Table 3. Effects of Other Drugs on Metoclopramide**

<b>Antipsychotics</b>	
<i>Clinical Impact</i>	Potential for additive effects, including increased frequency and severity of tardive dyskinesia (TD), other extrapyramidal symptoms (EPS), and neuroleptic malignant syndrome (NMS).
<i>Intervention</i>	Avoid concomitant use [see <i>Warnings and Precautions (5.1, 5.2, 5.3)</i> ].
<b>Strong CYP2D6 Inhibitors, not Included in Antipsychotic Category Above</b>	
<i>Clinical Impact</i>	Increased plasma concentrations of metoclopramide; risk of exacerbation of extrapyramidal symptoms [see <i>Clinical Pharmacology (12.3)</i> ].
<i>Intervention</i>	Reduce the metoclopramide tablet dosage [see <i>Dosage and Administration (2.2, 2.3)</i> ].
<i>Examples</i>	quinidine, bupropion, fluoxetine, and paroxetine
<b>Monoamine Oxidase Inhibitors</b>	
<i>Clinical Impact</i>	Increased risk of hypertension [see <i>Warnings and Precautions (5.5)</i> ].
<i>Intervention</i>	Avoid concomitant use
<b>Central Nervous System (CNS) Depressants</b>	
<i>Clinical Impact</i>	Increased risk of CNS depression [see <i>Warnings and Precautions (5.8)</i> ].
<i>Intervention</i>	Avoid metoclopramide tablets or the interacting drug, depending on the importance of the drug to the patient.
<i>Examples</i>	alcohol, sedatives, hypnotics, opiates and anxiolytics
<b>Drugs that Impair Gastrointestinal Motility</b>	
<i>Clinical Impact</i>	Decreased systemic absorption of metoclopramide.
<i>Intervention</i>	Monitor for reduced therapeutic effect.
<i>Examples</i>	antiperistaltic antidiarrheal drugs, anticholinergic drugs, and opiates
<b>Dopaminergic Agonists and Other Drugs that Increase Dopamine Concentrations</b>	
<i>Clinical Impact</i>	Decreased therapeutic effect of metoclopramide due to opposing effects on dopamine.
<i>Intervention</i>	Monitor for reduced therapeutic effect.

<i>Examples</i>	apomorphine, bromocriptine, cabergoline, levodopa, pramipexole, ropinirole, and rotigotine
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## 7.2 Effects of Metoclopramide on Other Drugs

Table 4 displays the effects of metoclopramide on other drugs.

**Table 4. Effects of Metoclopramide on Other Drugs**

<b>Dopaminergic Agonists and Drugs Increasing Dopamine Concentrations</b>	
<i>Clinical Impact</i>	Opposing effects of metoclopramide and the interacting drug on dopamine. Potential exacerbation of symptoms (e.g., parkinsonian symptoms).
<i>Intervention</i>	Avoid concomitant use [see <i>Warnings and Precautions (5.2)</i> ].
<i>Examples</i>	Apomorphine, bromocriptine, cabergoline, levodopa, pramipexole, ropinirole, rotigotine
<b>Succinylcholine, Mivacurium</b>	
<i>Clinical Impact</i>	Metoclopramide inhibits plasma cholinesterase leading to enhanced neuromuscular blockade.
<i>Intervention</i>	Monitor for signs and symptoms of prolonged neuromuscular blockade
<b>Drugs with Absorption Altered due to Increased Gastrointestinal Motility</b>	
<i>Clinical Impact</i>	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.
<i>Intervention</i>	<p><u>Drugs with Decreased Absorption (e.g., digoxin, atovaquone, posaconazole oral suspension *, fosfomycin):</u> 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).</p> <p><u>Drugs with Increased Absorption (e.g., sirolimus, tacrolimus, cyclosporine):</u> Monitor therapeutic drug concentrations and adjust the dose as needed. See prescribing information for the interacting drug.</p>
<b>Insulin</b>	
<i>Clinical Impact</i>	Increased GI motility by metoclopramide may increase delivery of food to the intestines and increase blood glucose.
<i>Intervention</i>	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.

## **8.2 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 tablets and any potential adverse effects on the breastfed child from metoclopramide 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 tablets are 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 tablets in pediatric patients have not been established.

Dystonias and other extrapyramidal symptoms associated with metoclopramide are more common in pediatric patients than in adults [see *Warnings and Precautions (5.1, 5.2)*]. In addition, neonates have reduced levels of NADH-cytochrome b<sub>5</sub> reductase, making them more susceptible to methemoglobinemia, a possible adverse reaction 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 metoclopramide tablets in elderly patients [see *Boxed Warning, Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)*].

#### **8.6 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 tablet 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)*].

#### **8.7 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 is no pharmacokinetic data in patients with moderate hepatic impairment (Child-Pugh B). Reduce metoclopramide tablet 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.

## 8.8 NADH-Cytochrome b<sub>5</sub> Reductase Deficiency

Metoclopramide-treated patients with NADH-cytochrome b<sub>5</sub> reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia. For patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with 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)*].

## 8.9 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 tablets [see *Clinical Pharmacology (12.3)*]. Reduce the metoclopramide tablet dosage in patients who are poor CYP2D6 metabolizers [see *Dosage and Administration (2.2, 2.3)*].

## 10 OVERDOSAGE

Manifestations of metoclopramide overdose 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 overdose. If over-exposure occurs, call your Poison Control Center at 1-800-222-1222 for current information on the management of poisoning or overdose.

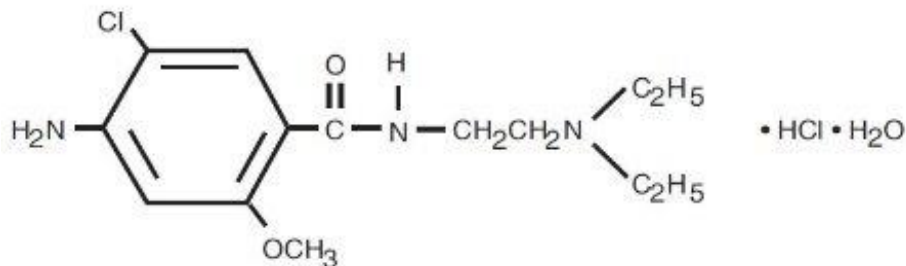
Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, which may be fatal.

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

## 11 DESCRIPTION

Metoclopramide hydrochloride, the active ingredient of metoclopramide tablets, is a dopamine-2 receptor antagonist. Metoclopramide hydrochloride (metoclopramide monohydrochloride monohydrate) is a white crystalline, odorless substance, freely soluble in water. Its chemical name is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate.

The molecular formula is C<sub>14</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>2</sub>•HCl•H<sub>2</sub>O. Its molecular weight is 354.3. The structural formula is:



Metoclopramide tablets are for oral administration. Metoclopramide tablets are available in 5 mg and 10 mg tablets.

Each tablet for oral administration contains metoclopramide hydrochloride, equivalent to either 5 mg or 10 mg metoclopramide. Tablets also contain as inactive ingredients anhydrous lactose, magnesium stearate, povidone, pregelatinized starch, sodium starch glycolate and (5 mg only) D&C Yellow #10 and FD&C Blue #1.

## 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 metoclopramide tablets 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

#### Absorption

Relative to an intravenous dose of 20 mg, the absolute bioavailability of oral metoclopramide is  $80\% \pm 15.5\%$  as demonstrated in a crossover study of 18 subjects. Peak plasma concentrations occurred at about 1 to 2 hours after a single oral dose. Similar time to peak was observed after individual doses at steady state.

In a single dose study of 12 subjects, the area under the drug concentration-time curve increased linearly with doses from 20 to 100 mg (5 times the maximum recommended single dose). Peak concentrations increased linearly with dose; time to peak concentrations remained the same; whole body clearance was unchanged; and the elimination rate remained the same. The mean elimination half-life in subjects with normal renal function was 5 to 6 hours. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

### 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

*Metabolism:* Metoclopramide undergoes enzymatic metabolism via oxidation as well as glucuronide and sulfate conjugation reactions in the liver. Monoethylmetoclopramide, 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 appeared 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) and 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) and 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 metoclopramide and 60 mg of fluoxetine (a strong CYP2D6 inhibitor) were administered, following prior exposure to 60 mg fluoxetine orally for 8 days. The patients who received concomitant metoclopramide and fluoxetine had a 40% and 90% increase in metoclopramide  $C_{max}$  and  $AUC_{0-\infty}$ , respectively, compared to patients who received metoclopramide alone (see Table 5) [see *Drug Interactions (7.1)*].

**Table 5. Metoclopramide Pharmacokinetic Parameters in Healthy Subjects with and without Fluoxetine**

<b>Parameter</b>	<b>Metoclopramide alone (mean ± SD)</b>	<b>Metoclopramide with fluoxetine (mean ± SD)</b>
C <sub>max</sub> (ng/mL)	44 ± 15	62.7 ± 9.2
AUC <sub>0-∞</sub> (ng·h/mL)	313 ± 113	591 ± 140
t <sub>1/2</sub> (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 in 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 three 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 Tablets, USP:

5 mg - Light green, round, unscored tablets

Debossed: **WPI** on one side and **2228** on the other side.

NDC 68071-4551-6 BOTTLES OF 6

NDC 68071-4551-8 BOTTLES OF 8

NDC 68071-4551-1 BOTTLES OF 10

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

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

## 17 PATIENT COUNSELING INFORMATION

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

Inform patients or their caregivers that metoclopramide tablets can cause serious adverse reactions. Instruct patients to discontinue metoclopramide 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 tablets.

Inform patients or their caregivers that metoclopramide 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)]* .

Manufactured by: Watson Pharma Private Ltd.  
Verna, Salcette Goa 403 722 INDIA

Distributed by: Impax Generics  
Hayward, CA 94544

1765-02  
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## MEDICATION GUIDE

### **Metoclopramide (MET oh KLOE pra mide) Tablets, USP,**

#### **Oral Use**

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

#### **What is the most important information I should know about metoclopramide tablets?**

**Metoclopramide 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 tablets. There is no treatment for tardive dyskinesia, but symptoms may decrease or go away over time after you stop taking metoclopramide tablets.

Your chances for getting tardive dyskinesia increase:

- the longer you take metoclopramide tablets and the more metoclopramide tablets you take. You should not take metoclopramide 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 healthcare provider to know if **you** will get tardive dyskinesia if you take metoclopramide tablets.

Call your healthcare provider right away if you get movements you cannot stop or control, such as:

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

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

### **What are metoclopramide tablets?**

Metoclopramide tablets are a prescription medicine used in adults:

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

Metoclopramide tablets are not recommended for use in children.

### **Do not take metoclopramide tablets if you:**

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

**Before taking metoclopramide tablets, tell your healthcare provider about all**

**of your medical conditions, including if you:**

- have diabetes. Your dose of insulin may need to be changed.
- had problems controlling your muscle movements after taking any medicine.
- have Parkinson's disease.
- have a type of tumor that can cause high blood pressure (pheochromocytoma).
- have kidney or liver disease.
- have or had depression or mental illness.
- have high blood pressure.
- have heart failure or heart rhythm problems.
- have breast cancer.
- drink alcohol.
- have seizures.
- are pregnant or plan to become pregnant. Metoclopramide may harm your unborn baby if taken during the end of pregnancy. Talk to your healthcare provider if you become pregnant while taking metoclopramide tablets.
- are breastfeeding or plan to breastfeed. Metoclopramide can pass into your breast milk and may harm your baby. You and your healthcare provider should decide if you will take metoclopramide tablets or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Metoclopramide may affect the way other medicines work, and other medicines may affect how metoclopramide works.

Tell your healthcare provider before you start or stop other medicines.

**Especially tell your healthcare provider if you take:**

- another medicine that contains metoclopramide, such as metoclopramide injection or metoclopramide oral solution
- a medicine for Parkinson's disease
- 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 healthcare provider or pharmacist.

**Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.**

**How should I take metoclopramide tablets?**

- Take metoclopramide tablets exactly as your healthcare provider tells you. Do not change your dose unless your healthcare provider tells you to.
- Metoclopramide tablets comes as a tablet you take by mouth.
- You should not take metoclopramide tablets for more than 12 weeks.
- Take metoclopramide tablets at least 30 minutes before each meal and at bedtime.
- If you take too many metoclopramide 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 tablets?**

- Do not drink alcohol while taking metoclopramide tablets. Alcohol may make some side effects of metoclopramide tablets worse, such as feeling sleepy.
- Do not drive, operate machinery, or do other dangerous activities until you know how metoclopramide tablets affect you. Metoclopramide tablets may cause sleepiness or dizziness.

### **What are the possible side effects of metoclopramide tablets?**

- **Tardive dyskinesia (abnormal muscle movements).** See “**What is the most important information I need to know about metoclopramide 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 less than 30 years of age.
  - **Parkinsonism.** Symptoms include slight shaking, body stiffness, trouble moving or keeping your balance. If you already have Parkinson's Disease, your symptoms may become worse while you are taking metoclopramide 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 your feet.
- **Neuroleptic Malignant Syndrome (NMS).** NMS is a very rare but very serious condition that can happen with metoclopramide 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 tablets become depressed, even if they have no history of depression. You may have thoughts about hurting or killing yourself. Some people who have taken metoclopramide tablets have ended their own lives (suicide).
- **High blood pressure.** Metoclopramide tablets can cause your blood pressure to increase.
- **Too much body water.** People who have certain liver problems or heart failure and take metoclopramide 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 tablets.

### **Call your healthcare provider 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 tablets include:

- restlessness
- drowsiness
- tiredness
- lack of energy

You may have more side effects the longer you take metoclopramide tablets and the more metoclopramide tablets you take.

You may still have side effects after stopping metoclopramide tablets. You may have symptoms from stopping metoclopramide tablets such as headaches, and feeling dizzy or nervous.

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of metoclopramide tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or Impax Laboratories, Inc. at 1-800-934-6729.

### **How should I store metoclopramide tablets?**

- Store metoclopramide tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep metoclopramide tablets in the bottle it comes in and away from light. Keep the bottle closed tightly.

**Keep metoclopramide tablets and all medicines out of the reach of children.**

### **General information about the safe and effective use of metoclopramide tablets.**

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

You can ask your pharmacist or healthcare provider for information about metoclopramide tablets that is written for health professionals.

### **What are the ingredients in metoclopramide tablets?**

**Active ingredient:** metoclopramide

**Inactive ingredients:**

**Metoclopramide 5 mg tablets:** anhydrous lactose, magnesium stearate, povidone, pregelatinized starch, sodium starch glycolate and D&C Yellow #10 and FD&C Blue #1.

**Metoclopramide 10 mg tablets:** anhydrous lactose, magnesium stearate, povidone, pregelatinized starch and sodium starch glycolate.

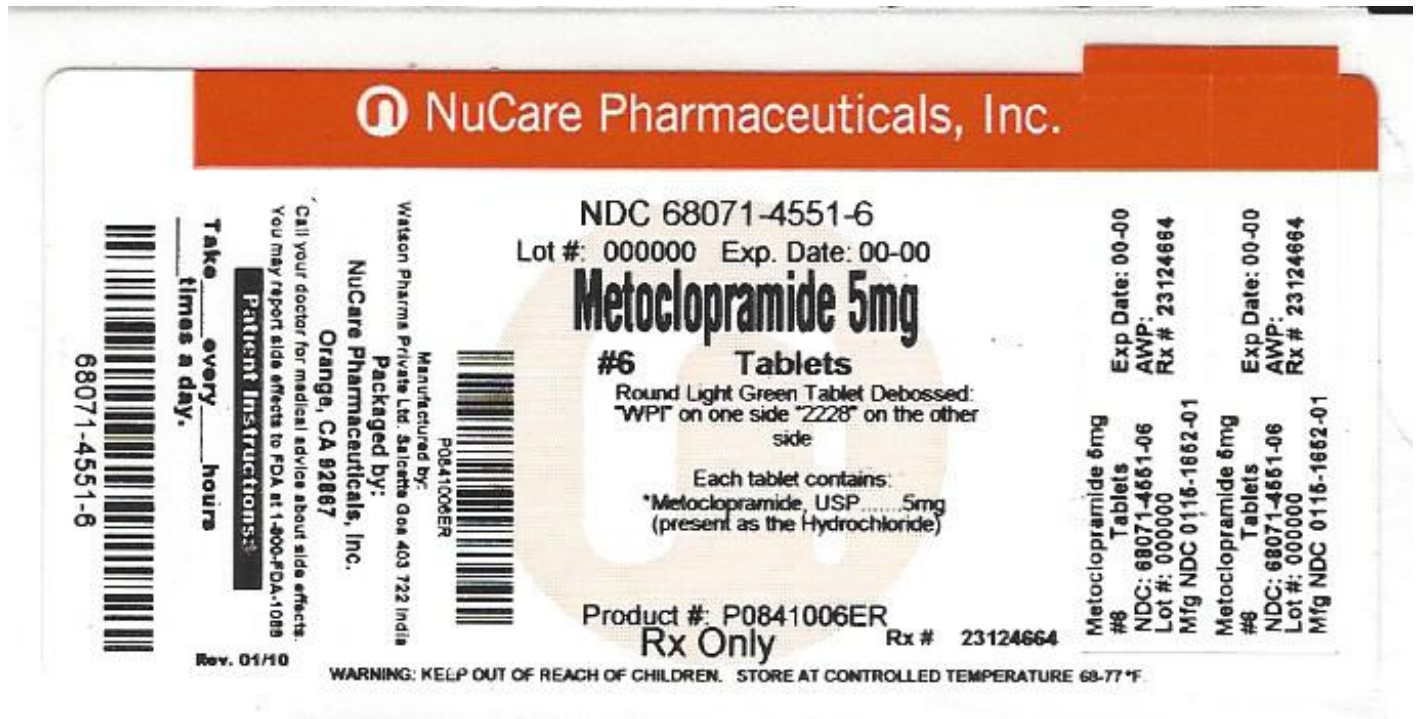
This Medication Guide has been approved by the U.S. Food and Drug Administration

Manufactured by: Watson Pharma Private Ltd.  
Verna, Salcette Goa 403 722 INDIA

Distributed by: Impax Generics  
Hayward, CA 94544

1765-02  
Rev. 09/2017

**PRINCIPAL DISPLAY PANEL -**



**METOCLOPRAMIDE HYDROCHLORIDE**

metoclopramide hydrochloride tablet

**Product Information**

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:68071-4551(NDC:0115-1652)
<b>Route of Administration</b>	ORAL		

**Active Ingredient/Active Moiety**

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

**Inactive Ingredients**

Ingredient Name	Strength
<b>ANHYDROUS LACTOSE</b> (UNII: 3SY5LH9PMK)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6130)	
<b>POVIDONE</b> (UNII: FZ989GH94E)	
<b>STARCH, CORN</b> (UNII: O8232NY3SJ)	
<b>SODIUM STARCH GLYCOLATE TYPE A POTATO</b> (UNII: 5856J3G2A2)	

**D&C YELLOW NO. 10** (UNII: 35SW5USQ3G)

**FD&C BLUE NO. 1** (UNII: H3R47K3TBD)

### Product Characteristics

<b>Color</b>	green (light green)	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	6mm
<b>Flavor</b>		<b>Imprint Code</b>	WPI;2228
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68071-4551-6	6 in 1 BOTTLE; Type 0: Not a Combination Product	09/06/2018	
2	NDC:68071-4551-8	8 in 1 BOTTLE; Type 0: Not a Combination Product	09/06/2018	
3	NDC:68071-4551-1	10 in 1 BOTTLE; Type 0: Not a Combination Product	09/06/2018	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072750	08/22/2011	

**Labeler** - NuCare Pharmaceuticals,Inc. (010632300)

### Establishment

Name	Address	ID/FEI	Business Operations
NuCare Pharmaceuticals,Inc.		010632300	repack(68071-4551)

Revised: 2/2021

NuCare Pharmaceuticals,Inc.