HIGHLIGHTS OF PRESCRIBING INFORMATION

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

GIMOTI™ (metoclopramide) nasal spray
Initial U.S. Approval: 1979

WARNING: TARDIVE DYSKINESIA

See full prescribing information for complete boxed warning.

- **Metoclopramide can cause tardive dyskinesia (TD), a serious movement disorder that is often irreversible. The risk of developing TD increases with duration of treatment and total cumulative dosage. (5.1)**
- **Discontinue GIMOTI in patients who develop signs or symptoms of TD. (5.1)**
- **Avoid treatment with metoclopramide (all dosage forms and routes of administration) for longer than 12 weeks because of the risk of developing TD with longer-term use. (5.1, 2.1)**

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

GIMOTI is a dopamine-2 (D_2) antagonist indicated for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis. (1)

Limitations of Use:

GIMOTI is not recommend 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)
- moderate or severe hepatic impairment (Child-Pugh B or C), moderate or severe renal impairment (creatinine clearance less than 60 mL/minute), and patients concurrently using strong CYP2D6 inhibitors due to the risk of increased drug exposure and adverse reactions. (1, 5.9, 7.1)

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

Administration

- See the full prescribing information for complete information on administration. (2.1)

Recommended Dosage

- *Adults less than 65 years of age:* The recommended dosage is 1 spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum of 4 sprays daily) for 2 to 8 weeks, depending on symptomatic response. (2.2)
- *Adults 65 years of age and older:* GIMOTI is not recommended in geriatric patients as initial therapy. Geriatric patients receiving an alternative metoclopramide product at a stable dosage of 10 mg four times daily can be switched to GIMOTI 1 spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum four times daily) for 2 to 8 weeks, depending on symptomatic response. (2.2, 8.5)

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

Nasal Spray: 15 mg metoclopramide in each 70 microliter spray. (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 GIMOTI 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 (≥5%) are: dysgeusia, headache, and fatigue. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Evoke Pharma, Inc. at 1-833-4-GIMOTI (1-833-444-6684), or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Antipsychotics: Potential for additive effects, including TD, EPS, and NMS; avoid concomitant use. (7.1)
- Central nervous system (CNS) depressants: Increased risk of CNS depression. Avoid concomitant use and monitor for adverse reactions. (7.1)
- Monoamine oxidase (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: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: TARDIVE DYSKINESIA

- **Metoclopramide can cause tardive dyskinesia (TD), a serious movement disorder that is often irreversible. The risk of developing TD increases with duration of treatment and total cumulative dosage *[see Warnings and Precautions (5.1)]*.**
- **Discontinue GIMOTI in patients who develop signs or symptoms of TD. In some patients, symptoms may lessen or resolve after metoclopramide is stopped *[see Warnings and Precautions (5.1)]*.**
- **Avoid treatment with metoclopramide (all dosage forms and routes of administration) 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 (2.1)]*.**

1 INDICATIONS AND USAGE

GIMOTI is indicated for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis.

Limitations of Use:

GIMOTI is 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)]*.
- moderate or severe hepatic impairment (Child-Pugh B or C), moderate or severe renal impairment (creatinine clearance less than 60 mL/minute), and patients concurrently using strong CYP2D6 inhibitors due to the risk of increased drug exposure and adverse reactions *[see Warnings and Precautions (5.9)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration and Storage Instructions

- Avoid treatment with metoclopramide (all dosage forms and routes of administration) for longer than 12 weeks because of the increased risk of developing TD with longer-term use *[see Warnings and Precautions (5.1)]*.
- One spray in one nostril administers the appropriate dose.
- Before administering the first dose from a bottle, prime the pump by pressing down on the finger flange and releasing 10 sprays in the air.
- Place the spray nozzle tip under one nostril and lean the head slightly forward so the tip of spray nozzle is aimed away from the septum and toward the back of the nose.
- Close the other nostril with the other index finger. Move spray pump upwards so the tip of the nozzle is in the nostril.
- To ensure a full dose, hold the bottle upright while pressing down firmly and completely on finger flange and release while inhaling slowly through the open nostril.
- Remove spray pump nozzle tip from nostril and exhale slowly through the mouth.
- Wipe the spray nozzle with a clean tissue.

Missed or Incomplete Doses

- If uncertain that the spray entered the nose, do not repeat the dose. Take the next dose at the scheduled time.
- If a dose is missed, take the next dose of GIMOTI at the regularly scheduled time. Do not make up for the missed dose or double the next dose.

Storage

Discard GIMOTI 4 weeks after opening even if the bottle contains unused drug.

2.2 Recommended Dosage

Adults Less Than 65 Years of Age: The recommended dosage of GIMOTI for the treatment of acute and recurrent diabetic gastroparesis in adults is 1 spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum of four times daily) for 2 to 8 weeks, depending on symptomatic response.

Adults 65 Years of Age and Older: Elderly patients may be more sensitive to the adverse effects of metoclopramide and require a lower starting dosage *[see Warnings and Precautions (5.1)]*. GIMOTI is not recommended in geriatric patients as initial therapy.

Geriatric patients receiving an alternative metoclopramide product at a stable dosage of 10 mg four times daily can be switched to GIMOTI 1 spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum four times daily) for 2 to 8 weeks, depending on symptomatic response. Avoid treatment with metoclopramide (all dosage forms and routes of administration) for longer than 12 weeks *[see Dosage and Administration (2.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Nasal Spray: 15 mg of metoclopramide in each 70 microliter spray. GIMOTI is an aqueous solution supplied in an amber glass bottle fitted with a metered spray pump attachment.

4 CONTRAINDICATIONS

GIMOTI 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. Metoclopramide 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 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 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 for longer than 12 weeks. GIMOTI is not recommended in geriatric patients as initial therapy *[see Dosage and Administration (2.2)]*.

Discontinue GIMOTI immediately in patients who develop signs and symptoms of TD. Consider treatment for established cases of TD, although in some patients TD may remit, partially or completely, within several weeks to months after GIMOTI is withdrawn.

Metoclopramide itself may suppress, or partially suppress, the signs of TD, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of TD is unknown. GIMOTI is contraindicated in patients with a history of TD *[see Contraindications (4)]*. Avoid GIMOTI 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 GIMOTI.

- Extrapyramidal symptoms (EPS), such as acute dystonic reactions, occurred in patients treated with oral 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 (GIMOTI 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 GIMOTI in patients receiving other drugs that can cause EPS (e.g., antipsychotics).
- Parkinsonian symptoms (bradykinesia, tremor, cogwheel rigidity, mask-like facies) have occurred after starting metoclopramide, more commonly within the first 6 months, but also after longer periods. Symptoms generally have subsided within 2 to 3 months after discontinuation of metoclopramide. Avoid GIMOTI in patients with Parkinson's disease and other patients being treated with antiparkinsonian drugs due to potential exacerbation of symptoms. Avoid treatment with metoclopramide (all dosage forms and routes of administration) for more than 12 weeks *[see Dosage and Administration (2.1), 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. Discontinue GIMOTI if these symptoms develop.

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 GIMOTI in patients receiving other drugs associated with NMS, including typical and atypical antipsychotics.

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

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

Management of NMS includes:

- Immediate discontinuation of GIMOTI 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 GIMOTI 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 GIMOTI 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. GIMOTI is contraindicated in patients with pheochromocytoma or other catecholamine-releasing paragangliomas *[see Contraindications (4)]*. Discontinue GIMOTI 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 GIMOTI if any of these adverse reactions occur.

5.7 Hyperprolactinemia

As with other dopamine D_2 receptor antagonists, metoclopramide elevates prolactin levels. Hyperprolactinemia may suppress hypothalamic gonadotropin-releasing hormone, 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_2 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 GIMOTI or the interacting drug, depending on the importance of the drug to the patient *[see Drug Interactions (7.1)]*.

5.9 Risk of Adverse Reactions with GIMOTI in Patients with Moderate or Severe Renal and Hepatic Impairment, CYP2D6 Poor Metabolizers and Patients Taking Strong CYP2D6 Inhibitors

Patients with moderate or severe renal or hepatic impairment, patients who are CYP2D6 poor metabolizers, and patients concurrently using strong CYP2D6 inhibitors have increased exposure to metoclopramide from GIMOTI due to reduced metabolism or excretion which may lead to an increased risk of adverse reactions, including tardive dyskinesia. Use of GIMOTI is not recommended in these patient populations since the dose of GIMOTI cannot be adjusted to reduce exposure *[*see *Drug Interactions (7.1), Use in Specific Populations (8.6, 8.7, 8.9)]*.

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 safety of GIMOTI was evaluated in clinical trials of patients with gastroparesis and established in clinical trials of oral metoclopramide.

Safety of GIMOTI

In a randomized, placebo-controlled clinical trial of 190 male and female patients of GIMOTI 14 mg, a slightly lower than recommended dosage, administered nasally four times daily for

4 weeks, dysgeusia was the most commonly reported adverse reaction (15% of GIMOTI-treated patients and 4% of placebo-treated patients). Other adverse reactions were similar to those reported for oral metoclopramide.

Safety of Oral Metoclopramide

The most common adverse reactions (in approximately 10% of patients receiving the recommended oral metoclopramide dosage of 10 mg 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 metoclopramide orally 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 1 displays the effects of other drugs on metoclopramide.

Table 1. 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	Use of GIMOTI is not recommended *[see Warnings and Precautions (5.9)]*.
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 GIMOTI or the interacting drug, depending on the importance of the drug to the patient.
Examples	alcohol, sedatives, hypnotics, opiates, and anxiolytics
Drugs that Impair Gastrointestinal Motility	
Clinical Impact	Decreased systemic absorption of metoclopramide.
Intervention	Monitor for reduced therapeutic effect.
Examples	antiperistaltic antidiarrheal drugs, anticholinergic drugs, and opiates
Dopaminergic Agonists and Other Drugs that Increase Dopamine Concentrations	
Clinical Impact	Decreased therapeutic effect of metoclopramide due to opposing effects on dopamine.
Intervention	Monitor for reduced therapeutic effect.
Examples	apomorphine, bromocriptine, cabergoline, levodopa, pramipexole, ropinirole, and rotigotine

7.2 Effects of Metoclopramide on Other Drugs

Table 2 displays the effects of metoclopramide on other drugs.

Table 2. Effects of Metoclopramide on Other Drugs

Dopaminergic Agonists and Drugs Increasing Dopamine Concentrations	
Clinical Impact	Opposing effects of metoclopramide and the interacting drug on dopamine. Potential exacerbation of symptoms (e.g., parkinsonian symptoms).
Intervention	Avoid concomitant use *[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 tablet.

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 a consistent pattern or a consistently increased risk of adverse pregnancy-related outcomes with oral use of metoclopramide during pregnancy. However, available data from a case report of GIMOTI use in pregnancy is insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

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 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 was observed.

8.2 Lactation

Risk Summary

There are no data on the presence of metoclopramide in human milk following nasal administration; however, published data report the presence of metoclopramide in human milk in variable amounts following oral administration *(see Data)*. Systemic exposure following nasal administration of GIMOTI 15 mg is expected to be similar to oral administration of metoclopramide 10 mg *[see Clinical Pharmacology (12.3)]*. Breastfed infants exposed to metoclopramide have experienced gastrointestinal adverse reactions, including intestinal discomfort and increased intestinal gas formation *(see Clinical Considerations)*. 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 GIMOTI and any potential adverse effects on the breastfed child from GIMOTI 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 oral 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 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 GIMOTI 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 Indications and Usage (1), Warnings and Precautions (5.1, 5.2)]*. In addition, neonates have reduced levels of NADH-cytochrome b_5 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 Warnings and Precautions (5.1), 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 adverse effects of metoclopramide, especially elderly women, and require a lower starting dosage. GIMOTI is not recommended in geriatric patients as initial therapy. Geriatric patients receiving an alternative metoclopramide product at a stable dosage of 10 mg four

times daily can be switched to GIMOTI *[see Dosage and Administration (2.2)]*.

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 *[see Clinical Pharmacology (12.3)]*. GIMOTI is not recommended in patients with moderate and severe renal impairment (creatinine clearance less than 60 mL/minute), including those receiving hemodialysis and continuous ambulatory peritoneal dialysis *[see Warnings and Precautions (5.9)]* Use the recommended dosage of GIMOTI in patients with mild renal impairment (creatinine clearance 60 mL/minute or greater) *[see Dosage and Administration (2.2)]*.

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 *[see Clinical Pharmacology (12.3)]*. 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). GIMOTI is not recommended in patients with moderate or severe (Child-Pugh B or C) hepatic impairment *[see Warnings and Precautions (5.9)]*. Use the recommended dosage of GIMOTI in patients with mild hepatic impairment (Child-Pugh A) *[see Dosage and Administration (2.2)]*.

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_5 Reductase Deficiency

Metoclopramide-treated patients with NADH-cytochrome b_5 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 *[see Clinical Pharmacology (12.3)]*. GIMOTI is not recommended in patients who are CYP2D6 poor metabolizers *[see Warnings and Precautions (5.9)]*.

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 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.

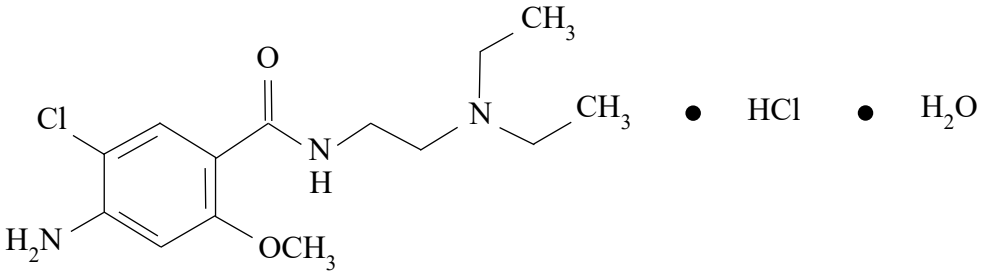
Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal.

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

11 DESCRIPTION

Metoclopramide hydrochloride, the active ingredient in GIMOTI, is a dopamine-2 receptor antagonist. Metoclopramide hydrochloride 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 $C_{14}H_{22}ClN_3O_2 \bullet HCl \bullet H_2O$. Its molecular weight is 354.3. The structural formula is:



GIMOTI (metoclopramide) nasal spray is for nasal administration. The product is supplied as an aqueous solution with a pH of 5.5 ± 0.5 in a 10 mL amber glass vial fitted with a metered spray pump attachment. Each unit contains 9.8 mL.

Each 70 microliter spray contains 15 mg metoclopramide, equivalent to 17.73 mg of metoclopramide hydrochloride. Inactive ingredients consist of benzalkonium chloride, citric acid monohydrate, edetate disodium dihydrate, purified water, sodium citrate dihydrate, and sorbitol.

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

Cardiac Electrophysiology

In a randomized, double-blind, positive-controlled thorough ECG study in 48 healthy subjects, a single administration of 80 mg metoclopramide nasal spray (approximately 5 times the recommended GIMOTI dose) had no effect on the QTc interval.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of metoclopramide following nasal administration of 10 mg metoclopramide is 47% in healthy subjects compared to intravenous injection of metoclopramide 10 mg. The systemic absorption after nasal administration is lower than that after oral administration given the same dose. Following nasal administration of GIMOTI 15 mg in healthy subjects, the systemic exposure (C_{max} and AUC) to metoclopramide and the time to reach C_{max} (T_{max}) were similar to orally administered 10 mg metoclopramide tablet.

After single nasal administration of metoclopramide at doses ranging from 10 mg to 80 mg in healthy subjects, there was a dose-proportional increase in the mean values for C_{max} and AUC.

The pharmacokinetic parameters of metoclopramide in healthy subjects following a single nasal administration of GIMOTI 15 mg are summarized in Table 3.

Table 3. Summary of Metoclopramide Pharmacokinetic Parameters in Healthy Subjects after a Single Nasal Administration of GIMOTI 15 mg

Parameter [a]	GIMOTI 15 mg
N	94
C_{max} (ng/mL)	41.0 (19.9)
t_{max} (h)	1.25 (0.50 – 3.50)
AUC_{0-t} (ng·h/mL)	349 (174.7)
AUC_{0-inf} (ng·h/mL) [b]	367 (184.8)
$t_{1/2}$ (h)	8.1 (2.0)

[a] Arithmetic mean (SD) except t_{max} for which the median (range) is reported.
[b] N = 93

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 mean elimination half-life in individuals with normal renal function is approximately 8 hours for administration with GIMOTI 15 mg.

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 Warnings and Precautions (5.9), 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 following oral administration in patients with moderate to severe renal impairment was about 2-fold the AUC in subjects with normal renal function. The AUC of metoclopramide in patients with ESRD on dialysis was about 3.5-fold the AUC in subjects with normal renal function *[see Warnings and Precautions (5.9), 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 after administration of oral metoclopramide *[see Warnings and Precautions (5.9), Use in Specific Populations (8.7)]*.

Sex and Body Weight: The AUC_{0-t} and C_{max} of metoclopramide were 34% and 42% higher in females than in males, respectively, following administration of metoclopramide nasal spray to healthy subjects. Based on population pharmacokinetic analysis, lean body weight (34.3 to 93.5 kg) has a significant impact on metoclopramide pharmacokinetics, with lower systemic exposure expected with higher lean body weight. The clinical significance of these findings is unknown.

Drug Interactions

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

Metoclopramide 20 mg was orally administered as a single dose to 24 healthy males, without (Period 1) and with (Period 2) a concomitant dose of fluoxetine 60 mg (a strong CYP2D6 inhibitor). Between the two periods, fluoxetine was administered orally for 8 days. The subjects who received concomitant metoclopramide and fluoxetine had a 40% and 90% increase in metoclopramide C_{max} and AUC_{0-inf}, respectively, compared to subjects who received metoclopramide alone. The mean half-life for metoclopramide was increased from 5.5 (±1.1) hours to 8.5 (±2.2) hours with concomitant fluoxetine *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.

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 6 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 MRHD 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 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.

14 CLINICAL STUDIES

The effectiveness of GIMOTI has been established based on studies of oral metoclopramide for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis.

16 HOW SUPPLIED/STORAGE AND HANDLING

GIMOTI (metoclopramide) nasal spray is supplied as a solution of metoclopramide in a 10 mL Type 1 amber glass bottle fitted with a metered spray pump attachment, a protective cap, and a safety clip. Each box of GIMOTI (NDC 72089-307-15) contains 1 bottle, with FDA-approved Patient Labeling (see Instructions for Use for proper actuation of the device).

Each actuation delivers 15 mg of metoclopramide. Each bottle contains 9.8 mL which is sufficient for 4 weeks of 4 times a day use.

Store at 20°C to 25°C (68°F to 77°F) excursions permitted 15°C to 30°C (59°F and 86°F) [*see USP Controlled Room Temperature*].

Discard GIMOTI 4 weeks after opening even if the bottle contains unused medicine.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Adverse Reactions

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

- Tardive dyskinesia and/or 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 the patient or their caregiver that metoclopramide can cause drowsiness or dizziness, or otherwise impair the mental and/or physical abilities required for the performance of hazardous

tasks such as operating machinery or driving a motor vehicle *[see Warnings and Precautions (5.8)]*.

Drug Interactions

Inform the 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 GIMOTI.

Administration Instructions *[see Dosage and Administration (2.1)]*

Advise the patients or their caregiver to read the *Instructions for Use* on how to appropriately administer GIMOTI:

- Avoid treatment with metoclopramide (all dosage forms and routes of administration) for longer than 12 weeks because of the increased risk of developing TD with longer-term use *[see Warnings and Precautions (5.1)]*.
- One spray in one nostril administers the appropriate dose.
- Before administering the first dose from a bottle, prime the pump by pressing down on the finger flange and releasing 10 sprays in the air.
- Place the spray nozzle tip under one nostril and lean the head slightly forward so the tip of spray nozzle is aimed away from the septum and toward the back of the nose.
- Close the other nostril with the other index finger. Move spray pump upwards so the tip of the nozzle is in the nostril.
- To ensure a full dose, hold the bottle upright while pressing down firmly and completely on finger flange and release while inhaling slowly through the open nostril.
- Remove spray pump nozzle tip from nostril and exhale slowly through the mouth.
- Wipe the spray nozzle with a clean tissue.

Missed or Incomplete Doses

- If uncertain that the spray entered the nose, do not repeat the dose. Take the next dose at the scheduled time.
- If a dose is missed, take the next dose of GIMOTI at the regularly scheduled time. Do not make up for the missed dose or double the next dose.

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