PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pms-METOCLOPRAMIDE TABLETS

Metoclopramide Tablets

Tablets, 5 mg and 10 mg, oral

USP

[Pr]pms-METOCLOPRAMIDE ORAL SOLUTION

Metoclopramide Oral Solution

Solution, 1 mg/mL, oral

USP

Antiemetic

Modifier of Upper Gastrointestinal Tract Motility

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

pms-METOCLOPRAMIDE TABLETS and pms-METOCLOPRAMIDE ORAL SOLUTION (metoclopramide hydrochloride) are indicated:

- As an adjunct in the management of delayed gastric emptying associated with subacute and chronic gastritis or following vagotomy, pyloroplasty and other surgical procedures.
- As an adjunct to facilitate small bowel intubation.
- As an adjunct to facilitate gastroduodenal evacuation of barium meals and to improve radiological visualization of the gastroduodenal region in patients with gastric atonia, pylorospasm, spasm of the duodenal bulb, or with mechanical gastric outlet obstruction. Metoclopramide has also been shown to accelerate small bowel transit of the barium meal and to facilitate fluoroscopy of the terminal ileum.
- To reduce postoperative vomiting induced by narcotics when used pre-operatively by the oral route.

1.1 Pediatrics

Pediatrics (≥ 5 year of age):

The efficacy and safety data on which the original indication was authorized to pediatric patients is not available. Health Canada has authorized an indication for pediatric use only for the treatment of delayed gastric emptying. (See 2 CONTRAINDICATIONS; 4.2 Recommended Dose and Dosage Adjustment).

Limitations of Use: pms-METOCLOPRAMIDE is not recommended for use in pediatric patients due to the risk of tardive dyskinesia and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates.

1.2 Geriatrics

Geriatrics (over 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

pms-METOCLOPRAMIDE is contraindicated in :

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with a history of tardive dyskinesia or a dystonic reaction to metoclopramide (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).
- Patients whenever stimulation of gastrointestinal motility might be dangerous, i.e., in the presence of gastrointestinal hemorrhage, mechanical obstruction or perforation.
- Patients with pheochromocytoma or other catecholamine-releasing paragangliomas. pms-METOCLOPRAMIDE may cause a hypertensive/pheochromocytoma crisis, probably due to release of catecholamines from the tumor.
- Patients with epilepsy.
- Patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.
- Children less than one year of age.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
TARDIVE DYSKINESIA

- Treatment with 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 dose.
- Metoclopramide therapy should be discontinued in patients who develop signs or symptoms of TD. There is no known treatment for TD. In some patients, symptoms may lessen or resolve after metoclopramide treatment is stopped.
- Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing TD.

For further information, see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance; 7 WARNINGS AND PRECAUTIONS, Neurologic, Extrapyramidal Symptoms; 8.5 Post-Market Adverse Reactions.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The total adult and pediatric daily dosage must not exceed 0.5 mg/kg/body weight.
- The recommended dosage of pms-METOCLOPRAMIDE should usually not be exceeded since a further increase in dosage will not produce a corresponding increase in clinical response.
- The duration of treatment with pms-METOCLOPRAMIDE should not exceed 12 weeks due to increased risk of developing tardive dyskinesia (TD) with longer-term use. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, and 7 WARNINGS AND PRECAUTIONS, Neurologic.
- A reduced dose of pms-METOCLOPRAMIDE should be considered in elderly patients, in patients with moderate or severe renal impairment, or with moderate or severe hepatic impairment. Dose adjustment is also recommended if some interacting drugs are concomitantly used (See 9.4 DRUG INTERACTIONS, Drug-drug interactions).

4.2 Recommended Dose and Dosage Adjustment

Health Canada has authorized an indication for children (5 to 14 years of age) only for the treatment of delayed gastric emptying (see 1.1 INDICATIONS, Pediatrics).

Dosage for Delayed Gastric Emptying

Adults and Children Over 14 Years of Age

Tablets: 5 to 10 mg 3 or 4 times a day before meals, depending upon response and body weight.

Oral solution: 5 to 10 mL (5 to 10 mg) 3 or 4 times a day before meals, depending upon response and body weight.

Children (5 to 14 Years of Age)

Tablets: 2.5 to 5 mg 3 times a day before meals, depending upon response and body weight.

Oral solution: 2.5 to 5 mL (2.5 to 5 mg) 3 times a day before meals, depending upon response and body weight.

Dosage for Small Bowel Intubation

Adults

Tablets: 10 mg by the oral route may be used, but has a greater period of latency than the i.v. route of administration.

Oral solution: 10 mL (10 mg) by the oral route may be used, but has a greater period of latency than the i.v. route of administration.

Dosage for Diagnostic Radiology

Adults

Tablets: 20 mg, 5 to 10 minutes before barium swallow.

Oral solution: 20 mL (20 mg), 5 to 10 minutes before barium swallow.

Dosage for Reduction of Post-Operative Vomiting Induced by Narcotics

Adults

Tablets: 20 mg, 2 hours before anaesthesia.

Oral solution: 20 mg (4 teaspoonfuls), 2 hours before anesthesia.

Special Populations and Conditions

Pediatrics

- pms-METOCLOPRAMIDE is contraindicated in children less than one year of age, and is not recommended for use in pediatric patients in general unless the anticipated benefits clearly outweigh potential risks. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; and 7.1.3 WARNINGS AND PRECAUTIONS, Pediatrics.
- The daily dose should not exceed 0.5 mg/kg, since with higher doses, extrapyramidal symptoms frequently occur.
- Extrapyramidal symptoms may also occur in children receiving the daily recommended dose of metoclopramide that should not exceed 0.5 mg/kg.

Geriatrics

- Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7.1.4 Geriatrics. Therefore, a reduced dose of pms-METOCLOPRAMIDE should be considered in elderly patients.

Renal Impairment

- The clearance of metoclopramide is decreased, and the systemic exposure is increased in patients with moderate to severe renal impairment (2-fold) compared to patients with normal renal function, which may increase the risk of adverse reactions. pms-METOCLOPRAMIDE dose should therefore be reduced 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 7 WARNINGS AND PRECAUTIONS, Renal and 10.3 Pharmacokinetics, Renal Insufficiency.

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). pms-METOCLOPRAMIDE dose should therefore be reduced in patients with moderate or severe (Child-Pugh B or C) hepatic impairment. No dose adjustment is required for patients with mild hepatic impairment (Child-Pugh A). See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and 10.3 Pharmacokinetics, Hepatic Insufficiency.

4.4 Administration

- pms-METOCLOPRAMIDE tablets should be swallowed whole with a drink of water.
- The dose of pms-METOCLOPRAMIDE oral solution is calculated as follows: each 5 mL (1 teaspoonful) contains 5 mg, e.g., a dose of 10 mg is equivalent to 10 mL or 2 teaspoons.
- Do not use two different forms of metoclopramide (tablets and oral solution) at the same time.

4.5 Missed Dose

If a dose is missed, patients are advised to take the dose as soon as remembered, unless it is almost time for the next dose. Patients are advised not to take extra medicine to make up the missed dose.

5 OVERDOSAGE

Symptoms:

Symptoms of overdosage may include drowsiness, disorientation, and extrapyramidal reactions. Anticholinergic or antiparkinsonian drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours.

Treatment:

Management of overdosage consists of gastric emptying, close observation and supportive therapy.

Hemodialysis removes relatively little metoclopramide, probably because of the small amount of the drug in blood relative to tissues. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of drug. It is unlikely that dosage would need to be adjusted to compensate for losses through dialysis. Dialysis is not likely to be an effective method of drug removal in overdose situations.

Methemoglobinemia has occurred in premature and full-term neonates who were given overdoses of metoclopramide (1-4 mg/kg/day orally, intramuscularly or intravenously for 1-3 or more days). Methemoglobinemia has not been reported in neonates treated with 0.5 mg/kg/day in divided doses. Methemoglobinemia can be reversed by the intravenous administration of methylene blue.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablets 5 mg and 10 mg	Colloidal Silicon Dioxide, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Polacrilin Potassium
oral	Oral Solution 1 mg/mL	Citric Acid, Glycerin, Methylparaben, Orange Natural & Artificial Flavour, Propylene Glycol, Propylparaben, Sodium Citrate, Sorbitol Solution, Purified Water

Description

Tablets:

- ***5 mg***: Each white, square, biconvex tablet is debossed "P" on one side and "M" over "5" on the other side. Available in HDPE bottles of 100 tablets.
- ***10 mg***: Each white, round, biconvex tablet is debossed "P" on one side and "M" scored "10" on the other side. Available in HDPE bottles of 100 tablets.

***Oral Solution*:**

- Available in HDPE bottles of 500 mL.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

In some patients, metoclopramide may produce sedation, drowsiness, galactorrhea, menstrual disorders and extrapyramidal reactions. Extrapyramidal symptoms are more frequent at higher than recommended doses, but may occur with therapeutic doses, particularly in children and in patients with impaired renal or hepatic function. Tardive dyskinesia has been reported following discontinuation of long-term treatment with metoclopramide (See 7 WARNINGS AND PRECAUTIONS, Neurologic, Extrapyramidal Symptoms).

The concomitant use of the following interacting drugs should be avoided as they may increase the risk of extrapyramidal effects: antipsychotics, monoamine oxidase inhibitors, central nervous system depressants, dopaminergic agonists and drugs increasing dopamine concentrations. The concomitant use of other interacting drugs may require to adjust the dose of pms-METOCLOPRAAMIDE or that of the interacting drugs. For more information, see 9.4 DRUG INTERACTIONS, Drug-Drug Interactions.

Carcinogenesis and Mutagenesis

Metoclopramide elevates prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies

conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time. See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity / Genotoxicity.

Cardiovascular

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.

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

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 pms-METOCLOPRAMIDE if any of these adverse reactions occur.

Dependence/Tolerance

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

Patients who discontinue treatment with metoclopramide due to signs and symptoms of tardive dyskinesia (TD) may continue to experience the same 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 is withdrawn.

Driving and Operating 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. The ambulatory patient should be cautioned accordingly.

Endocrine and Metabolism

As with other dopamine D2 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 (see 7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis). However, some clinical studies and epidemiology studies have not shown an association between administration of dopamine D2 receptor antagonists and tumorigenesis in humans.

Hepatic/Biliary/Pancreatic

Patients with severe hepatic impairment 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. The pms-METOCLOPRAMIDE dose should be reduced in patients with moderate or severe hepatic impairment (see 4.2 Recommended Dose and Dosage Adjustment, Hepatic Impairment).

By producing a transient increase in plasma aldosterone, metoclopramide may increase the risk of fluid retention in patients with hepatic impairment. Treated patients with hepatic impairment should be monitored for the occurrence of fluid retention and volume overload (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Neurologic

Extrapyramidal Symptoms

- *Tardive Dyskinesia (See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX)*

pms-METOCLOPRAMIDE is contraindicated in patients with a history of tardive dyskinesia (See 2 CONTRAINDICATIONS).

Tardive dyskinesia (TD) may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, and in patients with diabetes mellitus, it is not possible to predict which patients are likely to develop the syndrome. Therefore, a reduced dose of pms-METOCLOPRAMIDE should be considered in elderly patients.

Both risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible. Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided unless therapeutic benefit is thought to outweigh the risks to the patient developing TD.

There is no known treatment for established cases of TD although the syndrome may remit, partially or completely, within several weeks to months after metoclopramide has been withdrawn. pms-METOCLOPRAMIDE should be immediately discontinued in patients who develop signs and symptoms of TD.

Metoclopramide itself, however, 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 the syndrome is unknown.

- *Acute Dystonic Reactions*

pms-METOCLOPRAMIDE is contraindicated in patients with a history of a dystonic reaction to metoclopramide (see 2 CONTRAINDICATIONS).

Acute dystonic reactions occur in approximately 1 in 500 patients treated with the usual adult dosages of 30-40 mg/day of metoclopramide. These usually are seen during the first 24-48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less than 30 years of age and are even more frequent at the higher doses used in prophylaxis of vomiting due to cancer chemotherapy. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm. If these symptoms should occur, immediate treatment by health care professionals should be initiated to treat this condition.

- *Parkinsonian-like Symptoms*

Parkinsonian-like symptoms, including bradykinesia, tremor, cogwheel rigidity, or mask-like facies, have occurred more commonly within the first 6 months after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside within 2-3 months following discontinuance of metoclopramide. Patients with pre-existing Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

Neuroleptic Malignant Syndrome (NMS)

There have been rare reports of an uncommon but potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) associated with metoclopramide. Clinical manifestations of NMS include hyperthermia, muscle rigidity, altered consciousness, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac arrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. When these signs or symptoms occur, treatment with metoclopramide and other drugs not essential to concurrent therapy should be discontinued immediately. Intensive symptomatic treatment and medical monitoring should be initiated.

Avoid the use of metoclopramide in patients receiving other drugs associated with NMS, including typical and atypical antipsychotics.

Psychiatric

Mental depression has occurred in patients with and without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Renal

The clearance of metoclopramide is decreased, and the systemic exposure is increased (2-fold) in patients with moderate to severe renal impairment compared to patients with normal renal function, which may increase the risk of adverse reactions. pms-METOCLOPRAMIDE dose should therefore be reduced in patients with moderate and severe renal impairment (see 4.2 Recommended Dose and Dose Adjustment, Renal Impairment).

Reproductive Health: Female and Male Potential

As with other dopamine D2 receptor antagonists, metoclopramide elevates prolactin levels (hyperprolactinemia) which may lead to inhibition of reproductive function by impairing gonadal steroidogenesis in both female and male patients. Potential adverse reactions include galactorrhea, amenorrhea, gynecomastia, menstrual disorders, and impotence (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism; 8.1 Adverse Reaction Overview).

- **Fertility**

  While metoclopramide was found to have no effect on fertility in male and female rats, the effect of this medication on human fertility is unknown (see 7.1.1 Pregnant Women; 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

- **Function**

  Impotence (secondary to hyperprolactinemia) has been reported with prolactin-elevating drugs, including metoclopramide (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism). In animal studies, metoclopramide was found to have no effect on reproductive performance of male and female rats (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

- **Teratogenic Risk**

  No evidence of adverse developmental effects due to metoclopramide were observed in animal reproduction studies at 6 to 12 times the maximum recommended human dose (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

  The safe use of pms-METOCLOPRAMIDE in pregnancy has not been established. Therefore, metoclopramide should be used during pregnancy only when the potential benefits outweigh the possible risks to the fetus following exposure *in utero* to metoclopramide (see 7.1.1 Pregnant Women).

Sensitivity/Resistance

Reactions In patients with hypersensitivity to metoclopramide have included laryngeal and glossal angioedema and bronchospasm.

7.1 Special Populations

7.1.1 Pregnant Women

The safe use of pms-METOCLOPRAMIDE in pregnancy has not been established. Therefore, pms-METOCLOPRAMIDE should not be used in pregnant women, unless in the opinion of the physician the expected benefits to the patient outweigh the potential risks to the fetus.

Fetal/Neonatal Adverse Reactions: There are potential risks to the neonate following exposure *in utero* to metoclopramide during delivery; metoclopramide crosses the placental barrier and may cause extrapyramidal signs and methemoglobinemia in neonates with maternal administration during delivery. Neonates should be monitored for extrapyramidal signs (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Teratogenic Risk).

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.

7.1.2 Breast-feeding

Metoclopramide is excreted in human breast milk and could possibly harm the infant. Metoclopramide should only be used in breastfeeding women if the overall benefit outweighs the risk.

Monitor breastfeeding neonates because metoclopramide may cause extrapyramidal signs (dystonia) and methemoglobinemia. Breastfed infants exposed to metoclopramide have experienced gastrointestinal adverse reactions.

7.1.3 Pediatrics

- Metoclopramide is contraindicated in children under 1 year of age.
- Metoclopramide is not recommended for use in pediatric patients due to the risk of tardive dyskinesia and other extrapyramidal symptoms. It should not be used in children unless the anticipated benefits clearly outweigh potential risks. Safety and effectiveness of pms-METOCLOPRAMIDE in pediatric patients have not been established except to treat delayed gastric emptying in children 5 years of age and older (see 1.1 INDICATIONS, Pediatrics).
- Extra pyramidal symptoms may also occur in children receiving the daily recommended dose of metoclopramide that should not exceed 0.5 mg/kg (See 4.2 Recommended Dose and Dosage Adjustment).

- Dystonia and other extrapyramidal symptoms associated with metoclopramide are more common in pediatric patients than in adults. In addition, neonates have reduced levels of NADH-cytochrome b5 reductase, making them more susceptible to methemoglobinemia, a possible adverse reaction of metoclopramide use in neonates.

7.1.4 Geriatrics

Metoclopramide is known to be substantially excreted by the kidney, and the risk of adverse reactions, including tardive dyskinesia, may be greater in patients with impaired renal function (see 4.2 Recommended Dose and Dose Adjustment, Renal Impairment). Elderly patients are more likely to have decreased renal function and may be more sensitive to the therapeutic or adverse effects of metoclopramide; therefore, a reduced dose of pms-METOCLOPRAMIDE should be considered in elderly patients (see 1.2 Geriatrics; 3 SERIOUS WARNINGS AND PRECDAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS, Neurologic, Extrapyramidal Symptoms).

7.1.5 NADH-Cytochrome b5 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.

7.1.6 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 pms-METOCLOPRAMIDE (see 10.3 Pharmacokinetics, Special Populations and Conditions). The dose of pms-METOCLOPRAMIDE should be reduced in patients who are poor CYP2D6 metabolizers.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Many adverse reactions are described in other sections of the product monograph such as, tardive dyskinesia and other extrapyramidal effects, neuroleptic malignant syndrome, depression, hypertension, fluid retention, and effects on the ability to drive and operate machinery (See 3 SERIOUS WARNINGS AND PRECDAUTIONS BOX; 7 WARNINGS AND PRECAUTIONS).

In general, the incidence of adverse reactions correlates with the dose and duration of metoclopramide administration. Tardive dyskinesia, which in some cases appears to be irreversible, has been reported during long-term treatment (over 12 weeks) and following discontinuation of long-term metoclopramide therapy. Therefore, prolonged treatment with metoclopramide should be avoided. Tardive dyskinesia is characterized most frequently by involuntary movements of the tongue, face, mouth or jaw, and sometimes by involuntary movements of the trunk and/or extremities.

Drowsiness, fatigue and lassitude occur in approximately 10% of patients at the usual recommended dosage. Less frequent adverse reactions, occurring in approximately 5% of patients are insomnia, headache, dizziness and bowel disturbances.

Endocrine Disorders including galactorrhea, gynecomastia, impotence and menstrual disorders have also been reported.

The more serious adverse reactions associated with the use of metoclopramide are parkinsonism and/or other extrapyramidal reactions. These consist often of a feeling of restlessness, facial spasms, involuntary movements and in some cases, torticollis, muscular twitching, trismus, oculogyric crisis and opisthotonos.

8.2 Clinical Trial Adverse Reactions

The clinical trial data on which the original indication was authorized is not available.

8.5 Post-Market Adverse Reactions

- Dystonic reactions resembling tetanus have been reported.
- Extrapyramidal side effects appear to occur more frequently at higher than the usual recommended dosage.
- Tardive dyskinesia (TD), which in some cases appears to be irreversible, has been reported after discontinuation of long-term metoclopramide therapy. Less commonly, the TD syndrome can develop after relatively brief treatment periods at low doses. In some patients, symptoms may lessen or resolve after metoclopramide treatment is stopped. For further information, see 7 WARNINGS AND PRECAUTIONS, Neurologic, Extrapyramidal Symptoms and 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance.
- Other neurological reactions include convulsive seizures and 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.
- Hypersensitivity reactions, including anaphylaxis, bronchospasm and cutaneous reactions (rash, urticaria) have been reported especially in patients with a history of

asthma. Angioedema, including laryngeal, glossal, or periorbital edema, has been reported rarely.

- Cardiovascular events including atrioventricular block and cardiac arrest, acute congestive heart failure, hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention have been reported in association with the use of metoclopramide.
- Hepatotoxicity was reported when metoclopramide was administered with other drugs known to have hepatotoxic potential
- Hematologic events such as agranulocytosis, neutropenia, leukopenia, methemoglobinemia, and sulfhemoglobinemia have been reported.
- Other reactions include: urinary frequency disturbance and urinary incontinence, visual disturbances, and porphyria

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Anticholinergic drugs antagonize the effects of metoclopramide on gastrointestinal motility.

Metoclopramide should not be used in conjunction with ganglioplegic or neuroleptic drugs since potentiation of effects might occur.

The sedative effects of metoclopramide may be potentiated by sedatives, hypnotics, narcotics, and anxiolytics.

9.3 Drug-Behavioural Interactions

The effect of lifestyle choices (e.g. alcohol consumption, sexual activity, smoking) on the use of pms-METOCLOPRAMIDE has not been established.

9.4 Drug-Drug Interactions

Table 2 displays the effects of other drugs on metoclopramide.

Table 2 Effects of Other Drugs on Metoclopramide

Antipsychotics	
Clinical Impact	Potential for additive effects, including increased frequency and severity of tardive dyskinesia, other extrapyramidal symptoms, and neuroleptic malignant syndrome.
Intervention	Avoid concomitant use.
Strong CYP2D6 Inhibitors, not Included in Antipsychotic Category Above	

Clinical Impact	Increased plasma concentrations of metoclopramide; risk of exacerbation of extrapyramidal symptoms.
Intervention	Reduce the pms-METOCLOPRAMIDE dosage.
Examples	quinidine, bupropion, fluoxetine, and paroxetine
Monoamine Oxidase Inhibitors	
Clinical Impact	Increased risk of hypertension.
Intervention	Avoid concomitant use.
Central Nervous System (CNS) Depressants	
Clinical Impact	Increased risk of CNS depression.
Intervention	Avoid pms-METOCLOPRAMIDE 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, rotigotine

Table 3 displays the effects of metoclopramide on other drugs.

Table 3 Effects of Metoclopramide on Other Drugs

Dopaminergic Agonists and Drugs Increasing Dopamine Concentrations	
Clinical Impact	Opposing effects of metoclopramide and the interacting drug on dopamine. Potential exacerbation of symptoms (e.g., parkinsonian symptoms).
Intervention	Avoid concomitant use.
Examples	Apomorphine, bromocriptine, cabergoline, levodopa, pramipexole, ropinirole, rotigotine
Succinylcholine, Mivacurium	
Clinical Impact	Metoclopramide inhibits plasma cholinesterase leading to enhanced neuromuscular blockade.
Intervention	Monitor for signs and symptoms of prolonged neuromuscular blockade
Drugs with Absorption Altered due to Increased Gastrointestinal Motility	
Clinical Impact	The effect of metoclopramide on other drugs is variable. Increased gastrointestinal (GI) motility by metoclopramide may impact absorption of other drugs leading to decreased or increased drug exposure.

Intervention	*Drugs with Decreased Absorption (e.g., digoxin, atovaquone, posaconazole oral suspension*, fosfomycin)*: Monitor for reduced therapeutic effect of the interacting drug. For digoxin monitor therapeutic drug concentrations and increase the digoxin dose as needed (see prescribing information for digoxin). *Drugs with Increased Absorption (e.g., sirolimus, tacrolimus, cyclosporine)*: Monitor therapeutic drug concentrations and adjust the dose as needed. See prescribing information for the interacting drug.
Insulin	
Clinical Impact	Increased GI motility by metoclopramide may increase delivery of food to the intestines and increase blood glucose.
Intervention	Monitor blood glucose and adjust insulin dosage regimen as needed.

*Interaction does not apply to posaconazole delayed-release tablets

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Metoclopramide is a benzamide derivative, structurally related to procainamide and sulpiride. It has dopamine antagonist activity with selective affinity for D_2 (non-adenylate cyclase linked) receptors. It has been suggested that the behavioural, motor and neuroendocrine effects of metoclopramide are linked to its anti-dopaminergic activity.

10.2 Pharmacodynamics

Metoclopramide has antiemetic properties, which are believed to result from its action on the chemoreceptor trigger zone. A peripheral mechanism of action may also be involved.

Metoclopramide increases resting pressure in the lower esophageal sphincter and the gastric fundus, and gives rise to an increase in the amplitude of peristaltic movements in the

esophagus, gastric antrum and small intestine. These actions result in hastened esophageal clearance, accelerated gastric emptying and shortened transit time through the small bowel. These effects are blocked by atropine and opioids but not by vagotomy.

Metoclopramide elevates serum prolactin and causes transient increases in circulating aldosterone levels. These effects are thought to be due to blockade of dopamine receptors at the pituitary and adrenocortical cellular level.

Studies in rats, showed that parenteral administration of metoclopramide decreases striatal acetylcholine levels. The extrapyramidal side effects caused by metoclopramide and other neuroleptics may be a consequence of this action. Oral administration of metoclopramide to rats for 39 days induced behavioural supersensitivity to apomorphine and enhanced specific binding of ^{3}H-spiroperidol to striatal membranes. These effects are induced by other neuroleptic drugs, and are associated with a potential to elicit tardive dyskinesia in man.

10.3 Pharmacokinetics

Absorption

Bioavailability varies between 30 and 70%.

Distribution

Metoclopramide is not extensively bound to plasma proteins (about 15% to 20%). The whole-body volume of distribution is high (about 3.5 L/kg), which suggests extensive distribution of drug to the tissues.

Metabolism

There is a first-pass effect after oral administration. 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.

Elimination

Approximately 85% of the radioactivity of an orally administered dose appeared in the urine within 72 hours.

Special Populations and Conditions

- **Hepatic Insufficiency:** 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.

- **Renal Insufficiency:** 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.
- **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 $AUC_{0\text{-}inf}$, respectively, compared to patients who received metoclopramide alone.

11 STORAGE, STABILITY AND DISPOSAL

Tablets: Store between 15° and 30°C. Protect from light.

Oral solution: Store between 15° and 30°C. Protected from light and freezing.

Keep out of reach and sight of children.

Bring unused and expired prescription drugs to your local pharmacist for proper disposal.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

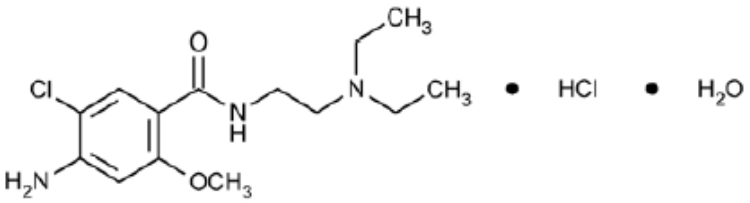
Proper name: Metoclopramide hydrochloride

Chemical name: 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxy benzamide, monohydrochloride, monohydrate;

or: 4-Amino-5-chloro-*N*-[2-diethylamino)ethyl]-*o*-anisamide monohydrochloride monohydrate

Molecular formula and molecular mass: $C_{14}H_{22}ClN_3O_2$ HCl H_2O / 354.28 g/mol

Structural formula:



Physicochemical properties: White or almost white crystalline powder, odourless, very soluble in water, freely soluble in alcohol, sparingly soluble in chloroform and insoluble in ether; melting point is 182.5–184°C.

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

A bioavailability study was performed to compare the rate and extent of absorption of a double dose (2 x 10 mg) of MAXERAN 10 mg tablets (Marion Merrell Dow Canada Inc.) *versus* pms-METOCLOPRAMIDE 10 mg tablets (Pharmascience Inc. Canada) in the fasting state. The results, summarized in the following table, demonstrate that the two drug products are bioequivalent.

Metoclopramide (2 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (ng·h/mL)	508.40 551.80 (43.5)	508.82 560.51 (47.8)	99.9	(95.1 - 105.0)
AUC_I (ng·h/mL)	561.43 616.31 (48.0)	560.26 624.68 (51.8)	100.2	(95.3 - 105.3)
C_{MAX} (ng/mL)	64.57 67.08 (28.3)	64.25 67.25 (31.4)	100.5	(95.5-105.8)
T_{MAX}§ (h)	1.10 (0.33)	1.30 (0.65)		
$T_{½}$§ (h)	6.26 (1.38)	6.44 (1.54)		

* pms-METOCLOPRAMIDE 10 mg tablets (Pharmascience Inc., Canada)
†MAXERAN 10 mg Tablets (Marion Merrell Dow Canada Inc.)
§Expressed as the arithmetic mean (standard deviation).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute toxicity

Animal species	Sex	Oral LD_{50} (95% probability inclusive of the 20% confidence limits) mg/kg
Albino mice*	F	660 (410-1063)
	M	385 (332-446)
	Combined	390 (361-421)
Albino rats**	F	550 (327-924)
	M	1000 (713-1402)
	Combined	830 (699-986)

* 14 groups, each with 5 animals/sex were treated with the test article at logarithmically spaced doses

** 6 groups, each with 5 animals/sex were treated with the test article at logarithmically spaced doses

Mortality generally occurred over a 4-hour period post-dosing in mice and a 24-hour period in rats. Systemic toxicity was generally characterized by lethargy and reduced motor activity in mice and rats and dyspnea, occasional tremor, twitching, pupillary dilatation, piloerection, hunching of the back, red lacrimation and epistaxis in rats.

Necropsy of these animals generally revealed reddening or darkening of liver and/or lungs in mice and rats and darkening of kidneys in rats. Several animals in the rat study showed distention of the stomach and/or intestines with red or yellow-red viscous material. In many cases, there was external evidence of perineal staining, epistaxis, lacrimation and/or ptyalism. Animals killed routinely at the conclusion of the study generally revealed no visible abnormality, although in a few mice darkening of lungs, spleen and/or liver was noted.

Subacute and Chronic Toxicity

In rats, which received metoclopramide in the diet, at levels of 10, 20 and 40 mg/kg for 77 weeks, gross weights were decreased in the mid- and high-dose groups. In purebred beagles which received 10, 20 or 40 mg/kg/day for 5 days a week for 54 weeks, miosis and fine and coarse tremors were seen in all drug-treated animals. Sedation and/or hyperactivity occurred occasionally. Tolerance did not develop. In general, the signs observed at all drug levels lasted approximately 3 to 5 hours after dosing. The severity increased gradually during the first 2 months of the study, then remained fairly constant until the end of the study. Frequent swallowing, panting and ptyalism occurred. There was a slight decrease of body weight and food consumption.

Carcinogenicity / Genotoxicity

Carcinogenicity

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.

Genotoxicity

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.

Reproductive and Developmental Toxicology

Reproduction studies in mice and rats dosed orally with 1, 5 or 10 mg/kg from day 1 to day 17 or 18 of gestation, respectively, disclosed no abnormalities and no effects of meto clopramide on fetal size and fetal weight.

Rabbits of the Fauve de Bourgogne strain were dosed orally with 10 or 20 mg metoclopramide from day 1 to day 25 of gestation. There was an apparent reduction in litter size in the group treated with 10 mg/kg. No effects were observed in young delivered spontaneously and raised to weaning. New Zealand albino rabbits received 5, 10 or 20 mg of metoclopramide/day in capsules from the 8th to 16th day of gestation. Offspring were delivered by caesarean section on day 29 or 30. Metoclopramide did not cause any adverse effects.

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.

Special Toxicology

In a drug interaction study, rabbits were pre-treated intramuscularly with either saline or phenylzine 15 mg/kg of body weight. (This dose of the MAO inhibitor is lethal in about 40% of rabbits). Twenty hours later, metoclopramide was administered intravenously at doses of 3.75, 7.50 and 15 mg/kg. Saline pre-treated rabbits showed only minimal symptomatology at the low- and mid-dose of metoclopramide; each of these doses of metoclopramide was lethal in 3 of 5 animals in phenylzine pre-treated rabbits. The high-dose metoclopramide was lethal

in 2 of 5 of the saline pre-treated, and in 5 of 5 of the phenylzine pre-treated rabbits. Thus, pre-treatment with phenylzine appeared to potentiate the toxicity of metoclopramide.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-METOCLOPRAMIDE TABLETS / [Pr]pms-METOCLOPRAMIDE ORAL SOLUTION

Metoclopramide Tablets / Metoclopramide Oral Solution

Read this carefully before you start taking **pms-METOCLOPRAMIDE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **pms-METOCLOPRAMIDE**.

Serious Warnings and Precautions

TARDIVE DYSKINESIA

- Treatment with metoclopramide can cause tardive dyskinesia (TD), a serious movement disorder that may become permanent. You are more likely to get TD if you take pms-METOCLOPRAMIDE at higher doses or for longer.
- There is no known treatment for TD. Stop taking pms-METOCLOPRAMIDE and get immediate medical help if you get any symptoms of TD. These include: muscle twitching or unusual / abnormal movement of the face or tongue or other parts of your body.
- Treatment with pms-METOCLOPRAMIDE for longer than 12 weeks should be avoided. Your healthcare professional will decide if you can take pms-METOCLOPRAMIDE for longer than 12 weeks.

What is pms-METOCLOPRAMIDE used for?

pms-METOCLOPRAMIDE is used along with other treatments:

- To manage slowed stomach emptying seen in people with gastritis and in those recovering from certain types of gastric tests or surgery.
- To help in bowel intubation procedures.
- To help in barium examinations of the stomach and other medical tests in patients with problems in their gastrointestinal tract (digestive system).
- To reduce vomiting that may occur after certain types of surgery.

How does pms-METOCLOPRAMIDE work?

pms-METOCLOPRAMIDE stimulates the muscles of the gastrointestinal tract. This helps speed the movement of food through the stomach and intestines.

What are the ingredients in pms-METOCLOPRAMIDE?

Medicinal ingredients: metoclopramide hydrochloride

Non-medicinal ingredients:

Tablets: Colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, polacrilin potassium.

Oral solution: Citric acid, glycerin, methylparaben, orange natural & artificial flavour, propylene glycol, propylparaben, sodium citrate, sorbitol solution, purified water.

pms-METOCLOPRAMIDE comes in the following dosage forms:

Tablets: 5 mg and 10 mg

Oral solution: 1 mg / mL

Do not use pms-METOCLOPRAMIDE if:

- You are allergic to metoclopramide hydrochloride or to any of the other ingredients in pms-METOCLOPRAMIDE.
- You have had tardive dyskinesia in the past.
- You experienced a movement disorder after treatment with metoclopramide.
- Whenever stimulation of gastrointestinal muscles might be dangerous, such as when there is gastrointestinal bleeding or other abnormal condition in your digestive system.
- You have a tumour in the adrenal gland.
- You have epilepsy.
- You are receiving other drugs which can produce side effects such as an inability to sit still, muscle contraction, tremors, stiff muscles, and facial movements (extrapyramidal reactions).

pms-METOCLOPRAMIDE should not be used in children less than one year of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-METOCLOPRAMIDE. Talk about any health conditions or problems you may have, including if you:

- have a history of bleeding (hemorrhage), a blockage (obstruction), or a tear (perforation) in your stomach or intestines
- have a history of seizures such as in epilepsy
- have Parkinson's disease
- have or have had breast cancer
- have liver, kidney, or heart problems
- have diabetes
- have or have had depression
- are over the age of 65 (you may need a reduced dosage)

Other warnings you should know about:

Tardive dyskinesia:

pms-METOCLOPRAMIDE can cause a condition called tardive dyskinesia. This is more likely to happen in patients who take pms-METOCLOPRAMIDE for longer than 12 weeks and in those taking a higher dose. You should not take it for longer than 12 weeks unless your doctor has told you to. However, it can also happen soon after starting pms-METOCLOPRAMIDE. Tardive dyskinesia happens more in elderly patients, especially women and in patients with diabetes mellitus. Stop taking pms-METOCLOPRAMIDE and get immediate medical help if you get any of the following symptoms of tardive dyskinesia: muscle twitching or unusual / abnormal movement of the face or tongue or other parts of your body. There is no known treatment for tardive dyskinesia. However, it may go away partly or completely after stopping treatment with pms-METOCLOPRAMIDE.

Pregnancy:

Tell your healthcare professional if you are pregnant, think you might be pregnant or are planning to become pregnant. It is not known if pms-METOCLOPRAMIDE is safe in pregnancy. You should not take pms-METOCLOPRAMIDE if you are pregnant unless your healthcare professional advises that you can.

Breastfeeding:

Tell your healthcare professional if you are breastfeeding or plan to breastfeed. pms-METOCLOPRAMIDE can pass into your breastmilk and harm your baby. Your healthcare professional will tell you if you can breastfeed your baby while taking pms-METOCLOPRAMIDE. If you do breastfeed while taking pms-METOCLOPRAMIDE, talk to your healthcare professional for how to monitor your baby for side effects.

Use in Children:

Metoclopramide must not be used in children under 1 year of age. Metoclopramide should not be used in children over 1 year of age unless the doctor believes the benefit outweighs the risk. Shaking, tremor, stiffness and involuntary movement may occur in children. If you observe these reactions in your child, contact your healthcare professional immediately. Children's dosage must not exceed 0.5 mg / kg / day.

Metoclopramide may cause side effects such as an inability to sit still, muscle contraction, tremors, stiff muscles, and unusual movements of the face. These effects are more common in children than in adults. Infants treated with metoclopramide may also develop a serious blood disorder which affects red blood cells.

Driving and Operating Machinery

Metoclopramide may affect your ability to drive and operate machinery. Use caution when operating a car or dangerous machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with pms-METOCLOPRAMIDE:

- antipsychotic drugs which are used to manage psychosis, such as risperidone, quetiapine, olanzapine, paliperidone, and clozapine.

- drugs used to treat depression such as bupropion, fluoxetine, and paroxetine
- monoamine oxidase inhibitors which are used to treat depression, such as phenelzine
- alcohol
- sedatives, sleep medication, narcotics, and other drugs that are used to treat anxiety such as phenobarbital, diazepam, clonazepam, and zolpidem
- digoxin, a heart medication
- drugs that increase dopamine concentrations and are used to treat various conditions such as Parkinson's disease (example: bromocriptine and levodopa)
- anti-peristaltic drugs, such as loperamide, which are used to treat diarrhea.

The use of other drugs may require your doctor to adjust your dose of pms-METOCLOPRAMIDE or the dose of the other drug that you are taking. For example, the dose of digoxin may have to be increased because metoclopramide can change the way your body absorbs digoxin.

How to take pms-METOCLOPRAMIDE:

- Take pms-METOCLOPRAMIDE exactly as your healthcare professional has told you to.
- If you do not understand the directions, ask your healthcare professional to explain them to you.
- Swallow pms-METOCLOPRAMIDE tablets whole with water.
- Do not use two different forms of metoclopramide (tablets and oral solution) at the same time.
- You should only take pms-METOCLOPRAMIDE for longer than 12 weeks if your healthcare professional has told you that you can.

Usual dose:

Note: The total daily dosage for adults and children must not exceed 0.5 mg / kg body weight.

Your healthcare professional will tell you how much pms-METOCLOPRAMIDE to take and when to take it. The amount you are given will be based on your response to the medicine, your age, your body weight and other safety considerations. Your doctor may also adjust your dose if you have kidney or liver problems.

Overdose:

If you think you, or a person you are caring for, have taken too much pms-METOCLOPRAMIDE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take another as soon as you remember, unless it is almost time for your next dose. Then go on as before. Do not take a double dose to make up for a missed dose.

What are possible side effects from using pms-METOCLOPRAMIDE?

These are not all the possible side effects you may have when taking pms-METOCLOPRAMIDE. If you experience any side effects not listed here, tell your healthcare professional.

Common side effects may include:

- drowsiness
- fatigue
- insomnia
- headache
- dizziness
- bowel disturbances

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Allergic reaction: rash, hives, breathing difficulty, swelling of the mouth, throat and extremities.			✓
Angioedema (swelling under the skin): redness, pain, or warmth in face, throat, arms, or hands, swelling of the face or mouth, difficulty breathing.		✓	
Blood problems: increase or decrease of white blood cells, abnormalities in red blood cells.		✓	
Endocrine Disorders: abnormal breast discharge, enlarged breast tissue in males, impotence, changes in the menstrual cycle.		✓	
Feeling depressed or thoughts about hurting or killing yourself.		✓	
Heart problems: shortness of breath, sudden chest pain, pressure or discomfort, dizziness, feeling faint, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise, high blood pressure.		✓	
Hepatotoxicity (liver damage):		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
yellowing of the skin and whites of the eyes, itching, abdominal pain, fatigue, loss of appetite, nausea, vomiting, rash, fever.			
Neuroleptic Malignant Syndrome (serious neurological condition): muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, confusion or reduced consciousness.			✓
Neurological reactions: convulsive seizures, hallucinations.		✓	
Parkinsonism or other extrapyramidal reactions (movement disorders): feeling restless, facial spasms, abnormal movements of head, jaw or eyeballs, muscular twitching, arching of the head, neck, and spine, slow movement, muscle stiffness, expressionless face.			✓
Problems with urination and bladder control.		✓	
Tardive Dyskinesia (movement disorder): muscle twitching or unusual / abnormal movement of the face or tongue or other parts of your body.			✓
Visual disturbance: double vision, blurred vision, floaters, flashes of light.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Tablets: Store between 15° and 30°C. Protect from light.

Oral solution: Store between 15° and 30°C. Protect from light and freezing.

Do not use after the expiry date shown on the bottle.

Keep out of reach and sight of children.

If you want more information about pms-METOCLOPRAMIDE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling the manufacturer's phone number, 1-888-550-6060.

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