PRODUCT MONOGRAPH

[Pr]APO-METOCLOP

Metoclopramide Hydrochloride Tablets Apotex Standard

5 and 10 mg

Modifier of Upper Gastrointestinal Motility

Antiemetic

APOTEX INC.
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THERAPEUTIC CLASSIFICATION

Modifier of Upper Gastrointestinal Motility
Antiemetic

ACTIONS AND CLINICAL PHARMACOLOGY

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.

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 also 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.

There is a first-pass effect after oral administration, and bioavailability varies between 30 to 70%. Metoclopramide is 15 to 20% bound to plasma proteins.

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.

INDICATIONS AND CLINICAL USE

APO-METOCLOP (metoclopramide hydrochloride) is useful as an adjunct in the management of delayed gastric emptying associated with subacute and chronic gastritis or following vagotomy, pyloroplasty, and other surgical procedures.

Metoclopramide has also been found useful as an adjunct to facilitate small bowel intubation.

Metoclopramide has been found useful 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.

Metoclopramide, when used pre-operatively by the oral route, may be useful in reducing post-operative vomiting induced by narcotics.

CONTRAINDICATIONS

APO-METOCLOP (metoclopramide hydrochloride) should not be used whenever stimulation of gastrointestinal motility might be dangerous, i.e., in the presence of gastrointestinal hemorrhage, mechanical obstruction or perforation. Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

Metoclopramide is contraindicated in children less than one year of age.

WARNINGS

WARNING:

Tardive dyskinesia has been reported to occur during long-term treatment (over 12 weeks) and following discontinuation of long-term treatment with metoclopramide.
The risk of developing tardive dyskinesia increases with the duration of treatment and the total cumulative dose. The elderly, especially elderly women are at increased risk of developing this condition.

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.

Metoclopramide should not be used in patients with epilepsy or extrapyramidal symptoms unless the expected benefits outweigh the risk of increased frequency and severity of seizures or extrapyramidal reactions.

Use in Pregnancy: The safe use of APO-METOCLOP (metoclopramide hydrochloride) in pregnancy has not been established. Therefore, 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.

Breastfeeding: 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.

Use in Children: The daily dose should not exceed 0.5 mg/kg, since with higher doses extrapyramidal symptoms frequently occur.

Tardive Dyskinesia

Tardive dyskinesia may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is not possible to predict which patients are likely to develop the syndrome.

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 tardive dyskinesia.

There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks to months after metoclopramide has been withdrawn.

Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long term course of the syndrome is unknown.

Other Extrapyramidal Symptoms (EPS)

Acute Dystonic Reactions

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). When these 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.

Depression

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.

Pediatrics

Metoclopramide is contraindicated in children less than one year of age.

Metoclopramide should not be used in children greater than 1 year of age unless the anticipated benefits clearly outweigh potential risks.

Extra pyramidal symptoms may also occur in children receiving the daily recommended dose of metoclopramide that should not exceed 0.5 mg/kg.

PRECAUTIONS

The recommended dosage of APO-METOCLOP (metoclopramide hydrochloride) should usually not be exceeded since a further increase in dosage will not produce a corresponding increase in clinical response.

Drug Interactions

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.

Metoclopramide may decrease the absorption of drugs from the stomach (e.g. digoxin) whereas absorption from the small bowel may be accelerated (e.g. acetaminophen, tetracyclines, levodopa, ethanol).

Care should be exercised when metoclopramide is administered in combination with a MAO inhibitor. In an animal study, pre-treatment with a MAO inhibitor increased the toxicity of i.v. metoclopramide.

In patients with pheochromocytoma, i.v. administered metoclopramide may cause a hypertensive crisis. These crises may be controlled by i.v. phenotolamine.

ADVERSE REACTIONS

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. Galactorrhea 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 opisthotonus. Dystonic reactions resembling tetanus have been reported. Extrapyramidal side effects appear to occur more frequently at higher than the usual recommended dosage. Tardive dyskinesia, which in some cases appears to be irreversible, has been reported after discontinuation of long-term metoclopramide therapy. Therefore, prolonged treatment with metoclopramide should be avoided.

Hypersensitivity reactions, including anaphylaxis, bronchospasm and cutaneous reactions (i.e. 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

Atrioventricular block and cardiac arrest has been reported in association with the use of metoclopramide.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Center immediately.

Symptoms: Symptoms of overdosage may include drowsiness, disorientation, and extrapyramidal reactions. Anticholinergic or antiparkinson 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.

DOSAGE AND ADMINISTRATION

Note: **The total adult and pediatric daily dosage must not exceed 0.5 mg/kg/body weight.**

For Delayed Gastric Emptying

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

Children (5 to 14 years): 2.5 to 5 mg 3 times a day before meals, depending upon response and body weight.

For Small Bowel Intubation

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

Use in Diagnostic Radiology

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

For the Reduction of Post-operative Vomiting Induced by Narcotics

Adults: 20 mg, 2 hours before anesthesia.

Use in Patients with Renal or Hepatic Impairment
Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 mL/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

See SYMPTOMS AND TREATMENT OF OVERDOSAGE section for information regarding dialysis.

Metoclopramide undergoes minimal hepatic metabolism, except for simple conjugation. Its safe use has been described in patients with advanced liver disease whose renal function was normal.

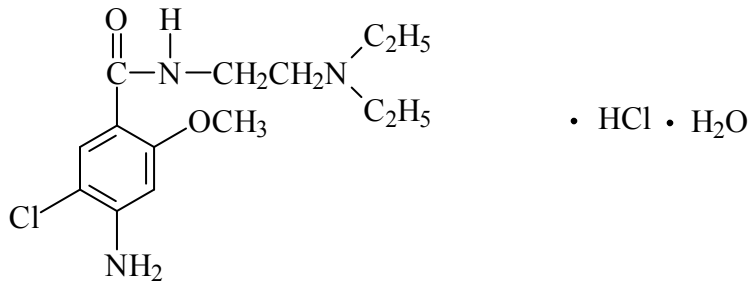
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Metoclopramide hydrochloride

Chemical Name: 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-*o*-anisamide monohydrochloride monohydrate

Structural Formula:



Molecular Formula: $C_{14}H_{22}ClN_3O_2 \bullet HCl \bullet H_2O$

Molecular Weight: 354.27

Description: White or practically white, crystalline, odorless or practically odorless powder. Very soluble in water; freely soluble in alcohol; sparingly soluble in chloroform; practically insoluble in ether.

Composition

In addition to metoclopramide hydrochloride, each tablet contains the non-medicinal ingredients lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

Stability and Storage Recommendations

Tablets should be stored at controlled room temperature (between 15 and 30º C) in tight light resistant containers.

AVAILABILITY OF DOSAGE FORMS

APO-METOCLOP 5 mg: Each square, white, biconvex tablet, engraved APO over M5 on one side, contains 5 mg of metoclopramide hydrochloride. Available in bottles of 100 and 500, and in unit dose packages of 100 (10x10).

APO-METOCLOP 10 mg: Each round, white, biconvex tablet, scored and engraved APO over M10 on one side contains 10 mg of metoclopramide hydrochloride. Available in bottles of 100 and 500, and in unit dose packages of 100 (10x10).

PHARMACOLOGY

Metoclopramide is a dopamine antagonist which appears to block preferentially the D-2 (non-adenylate cyclase linked) receptors.

In the rat, metoclopramide antagonizes apomorphine-induced stereotypy, causes catalepsy, elevates prolactin, aldosterone and plasma renin levels, and enhances dopamine turnover in mesolimbic and striatal structures.

Metoclopramide antagonizes in vitro the dopamine-induced inhibition of potassium-evoked ^{3}H acetylcholine release in striatal structures. In the rat, 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.

In experimental animals, metoclopramide enhances gastrointestinal motility, increasing both resting muscle tension and the amplitude of peristaltic movements. Metoclopramide also is a potent antagonist of vomiting induced by apomorphine, hydergine, tetrodotoxin and copper sulfate. Its mechanism of action appears to be by blockade of dopamine receptors in the chemoreceptor trigger zone. In the cat, spontaneous electrical discharges from this zone are stimulated by apomorphine and abolished by metoclopramide.

Metoclopramide is virtually inactive as an antagonist at the D-1 (adenylate cyclase linked) dopamine receptors, and is without potency in displacing radiolabeled ligands in receptor models designed to evaluate antipsychotic potential.

In the rat, intraventricular administration of metoclopramide and spiroperidol produce comparable dose-dependent depression of responding in electrical self-stimulation procedures. When administered by the intraperitoneal route, the potency of metoclopramide, but not that of spiroperidol, is decreased by a factor of 30.

TOXICOLOGY

Acute Toxicity

Animal Species	Sex	Oral LD_{50} (and 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.

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.

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 metoclopramide on fetal size and fetal weight.

Rabbits of the Fauve de Bourgogne strain were dosed orally with 10 or 20 mg of 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 cesarean section on day 29 or 30. Metoclopramide did not cause any adverse effects.

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CONSUMER INFORMATION

PrAPO-METOCLOP

Metoclopramide Hydrochloride Tablets

This leaflet is part of a "Product Monograph" published when APO-METOCLOP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-METOCLOP. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

APO-METOCLOP is a drug used to treat symptoms of slowed stomach emptying seen in people with gastritis, and in those recovering from certain types of gastric tests or surgery.

APO-METOCLOP, when used before surgery, can help reduce vomiting after surgical procedures.

What it does:

APO-METOCLOP is a drug used to help speed the movement of food through the stomach and intestines, by stimulating the muscles of the gastrointestinal tract.

When it should not be used:

Do not take APO-METOCLOP if you:

- are allergic (hypersensitive) to metoclopramide or any of the other ingredients listed in "**What the non-medicinal ingredients are."**
- are experiencing bleeding (hemorrhage), a blockage (obstruction), or a tear (perforation) in your stomach or intestines
- metoclopramide should not he used in children less than 1 year of age

What the medicinal ingredient is:

The active substance of APO-METOCLOP is metoclopramide hydrochloride.

What the important nonmedicinal ingredients are:

The non-medicinal ingredients are: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

What dosage forms it comes in:

APO-METOCLOP is available in 5 mg and 10 mg tablets.

WARNINGS AND PRECAUTIONS

- **A condition called tardive dyskinesia (see description below) has occurred with long-term (over 12 weeks) use of metoclopramide and even after long-term treatment has been stopped. The chance of this occurring increases with duration of treatment, total cumulative dose and in the elderly, particularly elderly women.**

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.**
- **extrapyramidal symptoms (e.g. shaking, tremor, stiffness and involuntary movement) may occur m children. Children's dosage should not exceed 0.5 mg/kg/day.**

Before you use APO-METOCLOP be sure to tell your doctor or pharmacist 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 (e.g. epilepsy)
- are pregnant. APO-METOCLOP should not be taken in pregnancy unless your doctor believes the benefit outweighs the risk to the fetus.
- are breastfeeding. Metoclopramide can pass into the breast milk and harm your baby. Talk to your doctor about the best way to feed your baby if you take metoclopramide
- have ever been diagnosed with breast cancer
- have kidney problems
- have an adrenal gland tumour called pheochromocytoma

Contact your doctor immediately if the following occur while taking metoclopramide:

- You develop symptoms of tardive dyskinesia or dystonia with symptoms such as involuntary movement of lips, eyes, tongue, face, head and limbs.

- You develop Parkinson's symptoms such as tremor, restlessness, muscle rigidity, facial spasms, involuntary movements, and difficulty completing daily tasks.
- You develop symptoms of neuroleptic malignant syndrome with symptoms such as high temperature, muscle rigidity, irregular or fast heartbeat
- You feel depressed or have thoughts about hurting or killing yourself.

INTERACTIONS WITH THIS MEDICATION

Some medications may block the effects of APO-METOCLOP, such as anticholinergic drugs. APO-METOCLOP may intensify the effect of alcohol and drugs absorbed from the intestines, such as neuroleptics.

Interactions may occur with monoamine oxidase inhibitors (e.g. some drugs used to treat depression).

Some drugs may increase the risk of drowsiness with APO-METOCLOP, such as sedatives, hypnotics, narcotics, and anxiolytics.

APO-METOCLOP may decrease the absorption of drugs from the stomach (e.g. digoxin) whereas
absorption from the small bowel may be accelerated (e.g. acetaminophen, tetracyclines, levodopa, alcohol).

PROPER USE OF THIS MEDICATION

Usual dose:

Note: **The total adult and pediatric daily dosage must not exceed 0.5 mg/kg/body weight.**

For Delayed Gastric Emptying
Adults: 5 to 10 mg 3 or 4 times a day before meals, depending upon response, body weight, and kidney function.

Children (5 to 14 years): 2.5 to 5 mg 3 times a day before meals, depending upon response and body weight.

Depending how well you respond to treatment and safety considerations, your dosage of APO-METOCLOP may be increased or decreased by your doctor, as appropriate.

Overdose:

In case of drug overdose, contact a health care practitioner (or doctor), hospital emergency department or regional poison control centre, even if there are no symptoms.

Missed Dose: Take the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next scheduled dose. Do not take extra medicine to make up the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects
The most common side effects are drowsiness and fatigue.

Other possible common side effects include insomnia, headache, dizziness and bowel disturbances.

If any of these affects you severely, **tell your doctor**.

If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Muscular twitching		√	
	Restlessness		√	
	Facial Spasms or movements		√	
	Unusual eye movements		√	
	Involuntary or unusual movements		√	
	Muscle rigidity		√	
	Tremors		√	
	High temperature, fast or irregular heartbeat		√	
	Feeling depressed or thoughts about hurting or killing yourself		√	
	Hypersensitivity (allergic) reaction with symptoms such as rash, hives, breathing difficulty, swelling of the mouth, throat and extremities		√	

This is not a complete list of side effects. For any unexpected effects while taking APO-METOCLOP, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (between 15 and 30°C) in tight, light resistant containers.

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

Keep out of the reach and sight of children.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at:
http://www.apotex.ca/products.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.