1 METOCLOPRAMIDE-BAXTER (5mg/mL solution for injection)

Metoclopramide-Baxter 5mg/mL solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

Metoclopramide-Baxter solution for injection contains 10mg in 2mL metoclopramide hydrochloride anhydrous (as metoclopramide hydrochloride) equivalent to 5mg in 1mL.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Appearance

Metoclopramide-Baxter injection is a clear, colourless, sterile, preservative-free solution for injection. pH range between 3.0 and 5.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults (20 years or older)

- Relief of nausea and vomiting associated with migraine, cancer therapy (chemotherapy or radiation), malignant disease, labour, infectious disease and uraemia;
- control of post-operative vomiting;
- assist in small bowel intubation.

Metoclopramide is of little benefit for the prevention or treatment of motion sickness.

Young adults and children (over 1 year of age)

Metoclopramide should be restricted to the following conditions when used as second line therapy, when used to treat children and young adults under 20 years of age because of the risk of adverse effects.

- Severe intractable vomiting of known cause;
- vomiting associated with radiation therapy or intolerance to cytotoxic drugs;
- assist in small bowel intubation.

4.2 Dose and method of administration

*Each **Metoclopramide-Baxter** ampoule is for use in one patient on one occasion only. Contains no antimicrobial preservative.*

Metoclopramide-Baxter solution for injection is available as 10mg/2mL strength ampoules.

The dosage recommendations should be strictly adhered to in order to minimize the possibility of dystonic side effects. Metoclopramide should only be used after careful examination has excluded any underlying disorder (such as cerebral irritation) that may have induced the nausea and vomiting.

Total daily doses of metoclopramide should not normally exceed 0.5mg/kg bodyweight. This should be less (if possible) in children and young adults, when given by injection.

Usual dosage is as follows and should be administered by slow intravenous injection over 1 - 2 minutes or intramuscularly.

Adults (20 yrs or older): 10mg three times a day

Young adults (15 - 19 yrs):
Treatment of young adults should commence at the lower dosage, where stated.
5 – 10mg three times a day.

Children:
Treatment of children should commence at the lower dosage, where stated.

5 - 14 yrs:	2.5 – 5mg three times a day.
3 - 5 yrs:	2mg two to three times a day.
1 - 3 yrs:	1mg two to three times a day.
Under 1 year:	1mg twice a day.

For Diagnostic Purposes
A single dose of metoclopramide may be given 5 - 10 minutes prior to the examination.

Adults (20 yrs or older): 10 – 20mg

Young adults (15 – 19 yrs): 10mg

Children:	*9 - 14 yrs:*	5mg
	5 - 9 yrs:	2.5mg
	3 - 5 yrs:	2mg
	Under 3 yrs:	1mg.

Metoclopramide should not be given to children unless a clear indication has been established for its use. Children are at a greater risk of experiencing adverse reactions to metoclopramide.

Use in special patient populations
Elderly patients
To avoid adverse reactions strict adherence to dosage recommendations is advised and, where prolonged therapy is considered necessary, patients should be regularly reviewed.

Use in patients with renal impairment
Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40mL/min, therapy should be initiated at approximately one-half the usual dose. Subsequent dosage will depend on individual clinical response.

Use in patients with hepatic impairment
Metoclopramide undergoes hepatic metabolism via simple conjugation. Its safe use has been described in patients with advanced liver disease whose renal function was normal. It is suggested that therapy be initiated at half the recommended dose with subsequent dose adjustment being made as the individual response has been determined.

Method of administration
For instructions on adding to intravenous fluids before administration, see section 6.6

4.3 Contraindications

- Patients in whom increased gastrointestinal motility might be dangerous, e.g. presence of gastrointestinal haemorrhage, mechanical obstruction or perforation
- Phaeochromocytoma due to the possibility of a hypertensive crisis, probably due to release of catecholamines from the tumour

- known hypersensitivity to metoclopramide. Note: patients sensitive to procaine and procainamide may be sensitive to metoclopramide
- patients with porphyria
- metoclopramide should not be used in patients with epilepsy since it may increase the frequency and severity of seizures
- metoclopramide should not be administered to patients receiving other medications which are likely to cause extrapyramidal reactions, since the frequency and severity of extrapyramidal reactions may be increased.

4.4 Special warnings and precautions for use

Persistent tardive dyskinesia

Tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high dose therapy, especially females. The symptoms are persistent and can often at times appear to be irreversible. The syndrome is characterized by rhythmical involuntary movement of the tongue, face, mouth or jaw (e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movement of extremities. There is no known effective treatment for tardive dyskinesia; however, in some patient's symptoms may lessen or resolve after metoclopramide treatment is stopped. Antiparkinson agents usually do not alleviate the symptoms of this syndrome.

Although the risk of tardive dyskinesia with metoclopramide has not been extensively studied, one published study reported a tardive dyskinesia prevalence of 20% among patients treated for at least 3 months. Both the 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.

Metoclopramide therapy should routinely be discontinued in patients who develop signs or symptoms of tardive dyskinesia. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and, if the medication is stopped at that time, the syndrome may not develop. Tardive dyskinesia may remit, partially or completely, within several weeks to months after metoclopramide is 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. Therefore, metoclopramide should not be used for the symptomatic control of tardive dyskinesia.

Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided in all but rare cases where the therapeutic benefit is thought to outweigh the risk to the patient of developing tardive dyskinesia.

Other

Care should be exercised in patients being treated with other centrally active drugs.

Since extrapyramidal symptoms may occur with both metoclopramide and neuroleptics such as phenothiazines, care should be exercised in the event of both drugs being prescribed concurrently (see section 4.5). The frequency and severity of seizures or extrapyramidal reactions may be increased in epileptic patients given metoclopramide.

Dystonic reactions

Dystonic reactions occur in approximately 1% of patients given metoclopramide. These occur more often in children and young adults and may occur after a single dose.

Neuroleptic malignant syndrome

Neuroleptic Malignant Syndrome has been reported when metoclopramide has been used alone, or in combination with neuroleptics (see section 4.8).

Prolactin levels

Metoclopramide elevates prolactin levels. This may be of importance in patients with previously detected breast cancer, in which the breast cancer is prolactin dependent. Although prolactin elevating drugs have been associated with disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence, the clinical significance of elevated serum prolactin levels is not known for most patients. Chronic administration of prolactin stimulating neuroleptic drugs to rodents has shown an increase in mammary neoplasms. However, neither clinical or epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorogenesis in humans and the available evidence is too limited to be conclusive at this time.

Metoclopramide-Baxter injection should be administered slowly over 1-2 minutes by intravenous injection to avoid a transient but intense feeling of anxiety and restlessness. Drowsiness may occur with rapid administration, so patients should be warned against engaging in activities requiring mental alertness for a few hours after the medicine has been administered.

Other

Patients with epilepsy may demonstrate an increased frequency or severity of seizures or extrapyramidal reactions if given metoclopramide.

Metoclopramide should be withheld for three to four days following gut surgery as vigorous muscular contractions may inhibit healing.

Special care should be taken in cases of severe renal insufficiency (see section 4.2).

The effects of metoclopramide may mask symptoms and delay the recognition of a serious disease. It should only be administered after a diagnosis has been established and should not be substituted for appropriate investigation of the patient's symptoms.

If vomiting persists in a patient being treated with metoclopramide, the patient's condition should be re- assessed to exclude the possibility of a more serious underlying disorder such as cerebral irritation.

Metoclopramide induced depression has been reported in patients without a prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide (see section 4.8). Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Metoclopramide should be used with caution in patients with hypertension as intravenously administered metoclopramide has been shown to release catecholamines.

Patients receiving prolonged treatment with metoclopramide should be reviewed regularly.

Metoclopramide can exacerbate parkinsonian symptoms; therefore, it should be used with caution, if at all, in patients with parkinsonian syndrome (see section 4.8).

Use in hepatic impairment

Refer section 4.2.

Use in renal impairment
Refer section 4.2.

Use in the elderly
To avoid adverse reactions adhere strictly to dosage recommendations and where prolonged therapy is considered necessary, patients should be regularly reviewed.

Effect on laboratory tests
Metoclopramide may blunt the response to the gonadorelin diagnostic test, by increasing serum prolactin levels. Metoclopramide may alter hepatic function test results.

4.5 Interaction with other medicines and other forms of interaction

Anticholinergic drugs and narcotic analgesics may antagonise the effects of metoclopramide on gastrointestinal motility.

Alcohol, sedatives, hypnotics, narcotics and tranquilisers have additive sedative effects when administered in conjunction with metoclopramide.

Due to its effects on gastric motility, metoclopramide may affect the rate of absorption of drugs from the gastrointestinal tract. Absorption of drugs such as paracetamol, aspirin in patients with migraine, cyclosporin, diazepam, dopamine, levodopa and morphine controlled release tablets which are mainly absorbed from the small bowel, may be accelerated. Absorption of drugs such as digoxin, bromocriptine, cimetidine, penicillin and quinidine which are mainly absorbed from the stomach may be decreased. Metoclopramide may cause extrapyramidal symptoms in some patients. Therefore, when metoclopramide is used concomitantly with other drugs that are likely to cause extrapyramidal reactions (e.g. neuroleptics such as phenothiazines), caution should be exercised.

The decrease in gastric emptying time caused by metoclopramide may increase the bioavailability of cyclosporin. Monitoring of cyclosporin concentrations may be necessary.

When metoclopramide is given concurrently with suxamethonium the recovery time is prolonged.

Since metoclopramide influences the delivery of food to the intestine and thus the rate of its absorption, the administration of metoclopramide may result in poor diabetic control in some patients. Therefore, adjustment in, or timing of, insulin dosage may be necessary in insulin-controlled diabetics.

The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

4.6 Fertility, pregnancy and lactation

Effects on fertility
No data available.

Use in pregnancy (Category A)
As there are no adequate or well controlled studies in pregnant women, metoclopramide should be used only if clearly needed. Animal tests in several mammalian species and clinical experience have not indicated any teratogenic effect. However, metoclopramide is not recommended during the first three months of pregnancy unless there are compelling reasons to do so.

Breast-feeding

As metoclopramide is excreted in human breast milk, its use is not recommended in nursing mothers unless the expected benefit outweighs the potential risk. The increased risk of adverse reactions in children should be considered when making a risk-benefit assessment.

4.7 Effects on ability to drive and use machines

Patients should be cautioned about engaging in activities requiring mental alertness for a few hours after the drug has been administered.

4.8 Undesirable effects

Neurological

Adverse reactions to metoclopramide that are most frequently seen are restlessness, drowsiness, fatigue and lassitude, which occur in approximately 10% of patients.

Less frequently, insomnia, headache, dizziness may occur. Rare (less than 1 in 1,000 cases) of acute depression have been reported. Symptoms of metoclopramide induced depression have ranged from mild to severe and have included suicidal ideation and suicide (see section 4.4). Anxiety or agitation may occur, especially after rapid injection. Delirium, severe dysphoria, obsessive rumination and mania have been reported occasionally.

Although uncommon at normal dosage, various extrapyramidal reactions to metoclopramide, usually of the dystonic type, have been reported. Acute dystonic reactions occur in approximately 0.2% of patients treated with 30 to 40mg of metoclopramide per day. In cancer chemotherapy patients receiving 1 to 2mg/kg per dose, the incidence is 2% in patients over the ages of 30 to 35, and 25% or higher in children and young adults who have not had prophylactic administration of diphenhydramine. Reactions include spasm of the facial muscles, trismus, rhythmic protrusion of the tongue, a bulbar type of speech, spasm of the extraocular muscles including oculogyric crisis, unnatural positioning of the head and shoulders and opisthotonos. There may be a generalised increase in muscle tone. The majority of reactions occur within 36 hours of starting treatment and the effects usually disappear within 24 hours of withdrawal of the drug. However, close observation is required and in cases of more severe reactions an antiparkinson drug such as benztropine or an anticholinergic antihistamine such as diphenhydramine should be given.

A fatal acute dystonic reaction has been reported in a patient who received hexamethylmelamine, cisplatin and metoclopramide high dose. Dystonic reactions may present rarely as upper airway obstruction with stridor and dyspnoea, possibly secondary to laryngospasm or supraglottic dystonia. A fatal cardiorespiratory arrest occurred in at least one patient with an acute dystonic reaction.

Tardive dyskinesia, which may be persistent, has been reported particularly in elderly patients (particularly women) following long-term therapy with metoclopramide. Tardive dyskinesia is most frequently characterised by involuntary movements of the tongue, face, mouth or jaw, and sometimes by involuntary movements of the trunk and/or extremities. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase with increasing duration of therapy and total cumulative dose. Although tardive dyskinesia can occur after relatively brief therapy with the drug at low doses, it appears to be more readily reversible under such circumstances (see section 4.4).

Very rare (less than 1 in 10,000) occurrences of neuroleptic malignant syndrome (NMS) have been reported. NMS is potentially fatal and comprises hyperpyrexia, altered consciousness, muscle rigidity, autonomic instability and elevated levels of CPK, and must be treated urgently (recognised treatments

include dantrolene and bromocriptine). Metoclopramide must be stopped immediately if NMS occurs.

Parkinsonian symptoms, including tremor, rigidity, bradykinesia and akinesia, occur rarely in patients receiving metoclopramide but may be associated with usual or excessive doses or with decreased renal function.

Gastrointestinal

Less frequently, nausea or bowel disturbances, may occur.

Cardiovascular

A single case of supraventricular tachycardia following intramuscular administration has been reported. There have been very rare (less than 1 in 10,000) cases of abnormalities of cardiac conduction (such as bradycardia and heart block) in association with intravenous metoclopramide. Hypertension, hypotension, cardiac arrest, atrial fibrillation, oedema, ventricular fibrillation, ventricular tachycardia, palpitations and tachycardia have also been associated with the use of metoclopramide. In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, caution should be exercised when metoclopramide is used in patients with hypertension.

Endocrine

Raised serum prolactin levels have been observed during metoclopramide therapy; this effect is similar to that noted with many other compounds. Galactorrhoea and breast enlargement have also been observed during metoclopramide therapy.

Hypersensitivity

There have been isolated reports of hypersensitivity reactions (such as urticaria, maculopapular rash) in patients receiving the metoclopramide.

Respiratory

Respiratory failure, secondary to dystonic reaction, acute asthmatic symptoms of wheezing and dyspnoea may occur.

Genitourinary

Urinary incontinence, sexual dysfunction, priapism and muscle spasm may also occur.

Other effects

There have been isolated reports of blood disorders. Methaemoglobinaemia, particularly following overdose in neonates, has also occurred in patients receiving metoclopramide. Agranulocytosis has also been observed.

General disorders

Hyperthermia has also been observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting (New Zealand) or at www.tga.gov.au/reproting-problems (Australia).

4.9 Overdose

Symptoms

Limited information is available on the acute toxicity of metoclopramide. Overdosage of metoclopramide may be expected to produce effects that are extensions of common adverse reactions: drowsiness, disorientation, and extrapyramidal reactions have been the principal effects reported. Other reported effects associated with metoclopramide overdosage have included feelings of anxiety or restlessness, headache, vertigo, nausea, vomiting, constipation, weakness, hypotension, and xerostomia; in addition generalized seizures and methaemoglobinaemia have occurred in infants. AV block has been observed very rarely.

Treatment

Treatment of metoclopramide overdose generally involves symptomatic and supportive care. There is no specific antidote for metoclopramide intoxication; however, agents with central anticholinergic activity (e.g. diphenhydramine, benztropine) may be useful in controlling extrapyramidal reactions. Symptoms of metoclopramide overdose are generally self-limiting and usually subside within 24 hours. Appropriate therapy should be instituted if hypotension or excessive sedation occurs. Methaemoglobinaemia should be treated with methylene blue. Haemodialysis or peritoneal dialysis is unlikely to enhance the elimination of metoclopramide.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Alimentary tract and metabolism, drugs for functional gastrointestinal disorders, propulsives.

ATC code

A03FA01.

Class

Antiemetic.

Mechanism of action

Metoclopramide has antiemetic, antinauseant and gastrokinetic activity. It stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary or pancreatic secretions. The rate of gastric emptying is increased due to increased peristalsis of the jejunum and duodenum. The tone and amplitude of gastric contractions are increased, with relaxation of the pyloric sphincter and duodenal bulb. These effects combine to result in decreased intestinal transit time. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs. Metoclopramide has little, if any, effect on the motility of the colon or bladder. Metoclopramide also exhibits dopamine antagonist activity and consequently produces sedation and, rarely, other extrapyramidal reactions. It may have serotonin receptor (5HT3) antagonist properties. Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and produces a transient increase in circulating aldosterone levels.

Clinical trials

No data available.

Appearance
Metoclopramide hydrochloride occurs as a white or almost white, crystalline powder or crystals, very soluble in water, freely soluble in alcohol, sparingly soluble in methylene chloride, practically insoluble in ether.

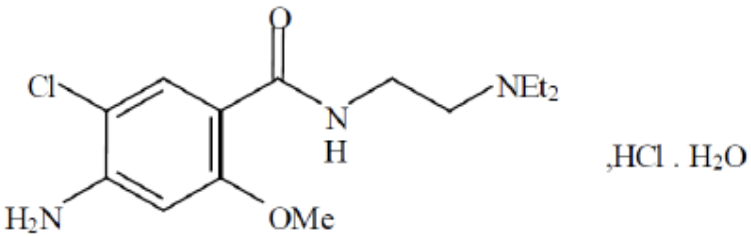
Chemical name
4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide hydrochloride monohydrate.

Molecular Formula
$C_{14}H_{22}ClN_3O_2.HCl.H_2O$

Molecular Weight
354.3

CAS Number
54143-57-6.

Structural formula



5.2 Pharmacokinetic properties

Absorption
Following intravenous administration, the onset of action is within 1 – 3 minutes and after intramuscular administration, this interval is extended to 10 – 15 minutes. The effect usually lasts from 1 – 2 hours.

Distribution
Plasma protein binding is 13 - 22%.

Metabolism
About 80% of the drug is excreted in the urine in the first 24 hours after administration. Approximately half is unchanged metoclopramide and half is the glucuronide and sulphate conjugate.

Excretion
Metabolism mainly occurs in the liver and elimination half-life may vary from 2.5 to 6 hours. Impaired renal function results in a reduced clearance and an increased half-life, up to 15 hours.

5.3 Preclinical safety data

Genotoxicity
No data available.

Carcinogenicity
No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Citric acid monohydrate
- Sodium citrate
- Sodium chloride
- Sodium hydroxide (for pH adjustment)
- Hydrochloric acid (for pH adjustment)
- Water for Injection
- Nitrogen.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

3 years.

The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

If ampoules are removed from their carton, they should be stored away from light. If inadvertent exposure occurs, ampoules showing a yellow discolouration must be discarded.

6.5 Nature and contents of container

Metoclopramide-Baxter solution for injection is available in type I clear glass ampoules of 2mL capacity (5s, 10s, 25s).

6.6 Special precautions for disposal and other handling

Compatibility

Intravenous fluids

No preservative is included in the formulation of Metoclopramide-Baxter solution for injection. Therefore, to reduce microbiological hazard, admixture to intravenous fluids should be performed under aseptic conditions and the infusion commenced as soon as possible after preparation and in any case within 24 hours of preparation. If storage is necessary, keep at 2 - 8°C.

The literature indicates that Metoclopramide-Baxter solution for injection may be added to the following solutions:

- Glucose 5% in sodium chloride 0.45%
- Glucose 5% in water
- Sodium chloride 0.9%
- Ringer's injection
- Ringer's injection, lactated (Hartmann’s solution).

Narcotic analgesics

- Morphine sulfate: 1mg/mL with metoclopramide hydrochloride 0.2mg/mL in Glucose 5% in water visually compatible for a 4 hour study period at 25°C under fluorescent light.
- Pethidine hydrochloride: 10mg/mL with metoclopramide hydrochloride 0.2mg/mL in Glucose 5% in water visually compatible for a 4 hour study period at 25°C under fluorescent light.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription only medicine.

8 SPONSOR

Metoclopramide-Baxter is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

Metoclopramide-Baxter is distributed in Australia by:

Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
18 October 2018.

10 DATE OF REVISION OF THE TEXT

7 November 2019.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Trade name changed. Consistent use of headings throughout and text rearranged for consistency with source document.
2	Excipients moved to 6.1.
3	pH range inserted.
4.2	Clarification of strength available for administration. Use in elderly patient's safety statement included.
4.4	Safety information relating to seizures or extrapyramidal reactions, anxiety and drowsiness, and use in elderly included.
4.7	Text updated for consistency with source document.
4.8	Safety information relating to Neuroleptic Malignant Syndrome updated, hyperthermia as general disorder added.
5.1	Pharmacotherapeutic group expanded and class added. Appearance included.
6.2	Section updated to be in alignment with source document.
6.6	Compatibility with narcotic analgesics include.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.