METOCLOPRAMIDE INJECTION AMPOULE
Metoclopramide hydrochloride 10 mg/2 mL

1. NAME OF THE MEDICINE

Metoclopramide hydrochloride monohydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metoclopramide Injection contains metoclopramide hydrochloride 10 mg in 2 mL (as monohydrate).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Metoclopramide Injection is a clear, colourless, sterile, preservative-free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

- Prevention of nausea and vomiting associated with chemotherapy and radiotherapy with low and minimal emetogenicity
- Prevention of post-operative nausea and vomiting (PONV)
- Symptomatic treatment of acute migraine induced nausea and vomiting
- Adjuvant to surgical and radiological procedures

Children (aged 1-18 years)

Treatment of established post-operative nausea and vomiting (PONV) as a second line option (intravenous use only).

4.2 Dose and method of administration

Dosage

The dosage recommendations should be strictly adhered to in order to minimise 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 nausea and vomiting.

For adults and children, the maximum dose in 24 hours is 0.5 mg per kg body weight with a maximum of 30 mg daily.

Maximum recommended treatment duration is 5 days in all age groups.

The solution can be administered intravenously (IV) or intramuscularly (IM).

Adults

The recommended single dose is 10 mg, repeated up to three times daily.

Prevention of PONV: a single dose of 10 mg is recommended.
Total daily doses of metoclopramide should not exceed 0.5 mg/kg bodyweight with a maximum of 30 mg daily.
The treatment duration should be as short as possible and switch to oral treatment should be made as soon as possible.

Treatment durations beyond 12 weeks should be avoided unless the therapeutic benefit is judged to outweigh the risk to the patient.

Please refer to dosing in Children section, below.

Children (aged 1-18 years)

The recommended dose is 0.10 to 0.15 mg/kg body weight, repeated up to three times daily by the intravenous route. The recommended maximum dose in 24 hours is 0.5 mg/kg body weight.

Dosing table

Age	**Body weight**	**Dose**	**Frequency**
1-3 years	10-14 kg	1 mg	Up to 3 times daily
3-5 years	15-19 kg	2 mg	Up to 3 times daily
5-9 years	20-29 kg	2.5 mg	Up to 3 times daily
9-18 years	30-60 kg	5 mg	Up to 3 times daily
15-18 years	Over 60 kg	10 mg	Up to 3 times daily

The injectable treatment duration should be as short as possible. The recommended maximum treatment duration is 48 hours for treatment of established post-operative nausea and vomiting (PONV).

Metoclopramide is contraindicated in children aged less than 1 year (see Section 4.3 Contraindications).

Due to the potential risk of severe cardiovascular reactions including cardiac arrest, the solutions for injection are restricted to be used only when appropriate resuscitation equipment is available (see Section 4.8 Adverse effects (undesirable effects), Cardiovascular).

Method of administration

IV doses should be administered as a slow bolus (at least over 3 minutes).

A minimum interval of 6 hours between two administrations is to be respected, even in case of vomiting or rejection of dose.

Dosage adjustment

Use in special patient populations

Elderly patients

In elderly patients, a dose reduction should be considered, based on renal and hepatic function and overall frailty.

Patients with renal impairment

In patients with severe renal impairment (creatinine clearance ≤15 mL/min), the daily dose should be reduced by 75%. In patients with moderate to severe renal impairment (creatinine clearance 15-60 mL/min), the dose should be reduced by 50%.

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. In patients with severe hepatic impairment, the dose should be reduced by 50%, with subsequent dose adjustment being made as the individual response has been determined.

Compatibility

Intravenous fluids

No preservative is included in the formulation of Metoclopramide 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°C to 8°C.

The literature indicates that Metoclopramide Injection may be added to the following solutions:
- Glucose 5% in sodium chloride 0.45%
- Glucose 5% in water
- Mannitol 20%
- Sodium chloride 0.9%
- Ringer's injection
- Ringer's injection, lactated (Hartmann's solution)

Narcotic analgesics

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

Cytotoxic drugs

If the standard formulation of metoclopramide is used for the treatment of nausea and vomiting associated with cytotoxic drugs, the cytotoxic agent should be administered as a separate infusion.

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 or intolerance 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 drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of extrapyramidal reactions may be increased
- Metoclopramide should not be used in children below 1 year of age
- Parkinson's disease

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 characterised 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 patients 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 risks to the patient of developing tardive dyskinesia.

Metoclopramide is associated with a risk of serious neurological adverse reactions such as irreversible tardive dyskinesia. The elderly are at higher risk of developing tardive dyskinesia following long-term treatment; in some cases this may be irreversible. Treatment should be kept as short as possible, in accordance to one's clinical judgment.

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 Interactions with other medicines and other forms of interactions). The frequency and severity of seizures or extrapyramidal reactions may be increased in epileptic patients given metoclopramide (see Section 4.3 Contraindications).

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 Adverse effects (undesirable effects)).

Prolactin levels

Metoclopramide elevates prolactin levels and the elevation persists during chronic administration (see Section 4.8 Adverse effects (undesirable effects)). This may be of importance in patients with previously detected breast cancer, in which the breast cancer is prolactin dependent. 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 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 tumorigenesis in humans and the available evidence is too limited to be conclusive at this time.

Other

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

The effects of metoclopramide may mask symptoms and delay the recognition of a serious disease. It should not be prescribed until 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 Injection should be administered slowly over 1-2 minutes by intravenous injection to avoid a transient but intense feeling of anxiety and restlessness, followed by drowsiness, which may occur with rapid administration.

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

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 Adverse effects (undesirable effects)). 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.

Use in hepatic impairment

In patients with clinically significant degrees of hepatic impairment, clearance of metoclopramide is likely to be reduced (see Section 4.2 Dose and method of administration, Dosage adjustment).

Use in renal impairment

In patients with clinically significant degrees of renal impairment, clearance of metoclopramide is likely to be reduced. Special care should be taken in cases of severe renal insufficiency (see Section 4.2 Dose and method of administration).

Paediatric use

Metoclopramide is contraindicated in children less than 1 year of age. 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 the elderly

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

Effects 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 Interactions with other medicines and other forms of interactions

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.

For compatibility with other medications, see Section 4.2 Dose and method of administration, Dosage adjustment and Section 6.2 Incompatibilities.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – 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.

Use in lactation

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 Adverse effects (undesirable effects)

Neurological

The most frequent adverse reactions to metoclopramide 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 Special warnings and precautions for use). 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 mg to 40 mg of metoclopramide per day. In cancer chemotherapy patients receiving 1 mg/kg to 2 mg/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 dystonic reaction has been reported in a patient who received hexamethylmelamine, cisplatin and high-dose metoclopramide. 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) undergoing 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 Special warnings and precautions for use).

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 should 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

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 (AF), oedema, ventricular fibrillation, tachycardia, ventricular tachycardia and palpitations 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 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.

Hepatic disorders

Rarely, cases of hepatotoxicity, characterised by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

Blood disorders

There have been isolated reports of blood disorders. Methaemoglobinaemia, particularly following overdose in neonates, has also occurred in patients receiving the drug. Neutropenia, leucopenia and agranulocytosis has been reported.

Sulfhaemoglobinaemia in adults has been reported.

General disorders

Hyperthermia has also been observed.

4.9 Overdose

Signs and 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 generalised seizures and methaemoglobinaemia have occurred in infants. AV block has been observed very rarely.

Treatment of overdosage

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of drug

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.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Plasma protein binding is 13% to 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

Sodium chloride;
Water for injections.

When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid.

6.2 Incompatibilities

See section 4.2 Dose and method of administration.

If the standard formulation of metoclopramide is used for the treatment of nausea and vomiting associated with cytotoxic drugs, the cytotoxic agent should be administered as a separate infusion.

6.3 Shelf life

Refer to outer carton.

6.4 Special precautions for storage

Store below 25°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 Injection 10 mg in 2 mL (sterile) Steriluer® ampoule (10s)

Metoclopramide Injection 10 mg in 2 mL (sterile) Steriluer® ampoule (50s)

Not all presentations may be available locally.

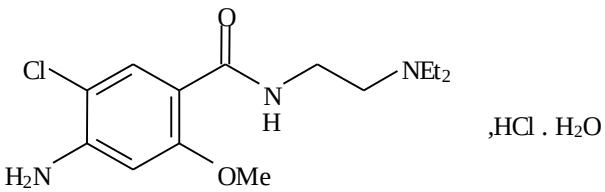
6.6 Physicochemical properties

Metoclopramide hydrochloride monohydrate 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

The structural formula is:

Chemical structure



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

Molecular Weight: 354.3

CAS Number

54143-57-6

7. NAME AND ADDRESS OF PRODUCT OWNER

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