Metoclopramide Injection BP 5mg/mL Product Information

DESCRIPTION

Each injection contains metoclopramide hydrochloride 5 mg/mL. The chemical name is 4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide hydrochloride monohydrate. CAS no: 54143-57-6.

![Chemical Structure]

The clear, colourless, particle free solution also contains sodium chloride and Water for Injections. The pH is adjusted with hydrochloric acid and ranges from 3.0 to 5.0.

PHARMACOLOGY

Metoclopramide hydrochloride is a substituted benzamide which stimulates the motility of the upper gastrointestinal tract without affecting gastric, biliary, or pancreatic secretion. Gastric peristalsis is increased by metoclopramide which leads to accelerated gastric emptying. Duodenal peristalsis is also increased, which decreases intestinal transit time. The gastro-oesophageal sphincter resting tone is increased, while the pyloric sphincter is relaxed. 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 possesses parasympathetic activity as well as being a dopamine-receptor antagonist with a direct effect on the chemoreceptor trigger zone. It may have serotonin-receptor (5HT₃) antagonist properties. Like other dopamine antagonists, metoclopramide produces sedation and may cause extrapyramidal reactions. Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and produces a transient increase in circulating aldosterone levels.
Pharmacokinetics

The onset of action following injection of metoclopramide hydrochloride is 1 to 3 minutes following intravenous administration, and 10 to 15 minutes following intramuscular administration. Pharmacological effects persist for 1 to two hours after onset.

Plasma protein binding ranges from 13 to 22%.

About 80% of metoclopramide is excreted in the urine in the first 24 hours, approximately half as the glucuronide and sulfate metabolites and half as unchanged drug. Elimination half-life can vary from 2.5 to 6 hours. Impaired renal function prolongs the half-life of metoclopramide by up to 15 hours due to reduced clearance.

INDICATIONS

ADULTS (≥ 20 years)
For the treatment of nausea and vomiting associated with migraine, cancer therapy (either chemotherapy or radiation), anaesthesia, labour, or infectious diseases.

To facilitate small bowel intubation procedures.

To stimulate gastric emptying during radiographic examinations.

Intramuscular administration of metoclopramide facilitates the absorption of a range of oral drugs in people with migraine.

Treatment of mild to moderate diabetic gastroparesis. Metoclopramide should only be used until diabetic control is established.

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

YOUNG ADULTS AND CHILDREN

Metoclopramide should be restricted to the following conditions 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 radiotherapy or intolerance to cytotoxic drugs.

To facilitate small bowel intubation procedures.

CONTRAINDICATIONS

1. Conditions where stimulation of gastric motility may be dangerous e.g. gastrointestinal haemorrhage, mechanical obstruction, perforation.
2. Phaeochromocytoma. Metoclopramide may cause a hypertensive crisis in patients with phaeochromocytoma, probably due to release of catecholamines from the tumour.

3. Metoclopramide should not be used in patients with porphyria.

4. Known hypersensitivity to metoclopramide. *Note: patients sensitive to procaine and procainamide may be sensitive to metoclopramide.

5. *Metoclopramide should not be used in patients with epilepsy since it may increase the frequency and severity of seizures.

6. *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.

PRECAUTIONS

1. Dystonia
   Approximately 1% of patients given metoclopramide have dystonic reactions. These occur more frequently in children (approximately 10% if < 10 years old) and young adults and may occur after a single dose.

2. Persistent tardive dyskinesia
   Some patients on long term therapy may develop tardive dyskinesia during or after treatment. Elderly patients on high dose therapy appear to be at greatest risk, particularly female elderly patients. The symptoms are persistent and in some patients appear to be irreversible. Rhythmic, involuntary movements of the tongue, face, mouth or jaw is characteristic. These can include protrusion of the tongue, puffing of the cheeks, puckering of the mouth and chewing movements. Involuntary movements of the extremities may also be present.

   There is no known effective treatment for tardive dyskinesia. Antiparkinson agents are usually ineffective in alleviating the symptoms. If the symptoms do appear the dose of metoclopramide, and all other antipsychotic or antidopaminergic agents should be reduced progressively until discontinued if possible.

   Fine vermicular movements of the tongue may be the first signs of tardive dyskinesia, and if medication is stopped on the appearance of these the syndrome may not develop.

3. Prolactin levels
   Metoclopramide raises prolactin levels after a single dose and keeps them raised during chronic administration. This should be borne in mind when metoclopramide treatment is considered in patients with previously diagnosed 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 for most patients is unknown.

Chronic administration of prolactin stimulating neuroleptic drugs to rodents have 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. The available evidence is too limited to be conclusive at this time.

4. **Epilepsy**  
Patients with epilepsy may demonstrate an increased frequency or severity of seizures or extrapyramidal reactions if given metoclopramide. *The frequency and severity of extrapyramidal reactions may be increased with neuroleptics such as phenothiazines.*

5. **Stomach operations**  
Following operations such as gut anastomosis or pyloroplasty, metoclopramide should not be given for three or four days, since vigorous muscle contractions may delay healing.

6. **Neuroleptic malignant syndrome**  
Metoclopramide is known to have caused fatal neuroleptic malignant syndrome.

7. **Depression**  
Metoclopramide-induced depression has been reported in patients without a prior history of depression. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

8. **Masking disease**  
The symptomatic relief provided by metoclopramide may delay recognition and diagnosis of disease. Diagnosis should be established prior to instituting metoclopramide treatment by appropriate investigations.

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

10. **Persistent vomiting**  
If vomiting persists in a patient being treated with metoclopramide, the patient should be reassessed to exclude the possibility of an underlying disorder such as cerebral irritation.

11. **Intravenous injection**  
When given by intravenous injection, metoclopramide should be administered over a 1 to 2 minute period. Rapid administration may produce a transient but intense feeling of anxiety and restlessness, followed by drowsiness.
12. **Mental alertness**
   Patients should be cautioned about engaging in activities requiring mental alertness (e.g. driving, operating machinery) for a few hours after the drug is administered.

13. **Hypertension**
   Intravenously administered metoclopramide has been shown to release catecholamines, therefore caution should be taken when metoclopramide is used in patients with hypertension.

14. **Regular review**
   Patients who are receiving prolonged treatment with metoclopramide should be reviewed regularly.

15. **Parkinson’s Disease**
   Metoclopramide can exacerbate parkinsonian symptoms, therefore it should be used with caution, if at all, in patients with parkinsonian syndrome.

16. **Renal Insufficiency**
   Special care should be taken in cases of severe renal insufficiency.

**Use in pregnancy  Category A**

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**

Metoclopramide is excreted in human breast milk. It is not known whether it has a harmful effect on the newborn. It is therefore not recommended for nursing mothers unless the benefits to the mother outweigh any potential risk to the child. The increased risk of adverse reactions in children should be considered when making a risk-benefit assessment.

**Interactions**

**Increased absorption**
Concomitant metoclopramide therapy increased the absorption or decreased the time to peak plasma levels of paracetamol, aspirin in patients with migraine, cyclosporin, diazepam, dopamine, levodopa, *tetracycline, lithium* and morphine controlled release tablets.

**Decreased absorption**
Concomitant metoclopramide therapy decreased the absorption or increased the time to peak plasma levels of acidic drugs, bromocriptine, cimetidine, digoxin, penicillin and quinidine.
*Cyclosporin
The decrease in gastric emptying time caused by metoclopramide may increase the bioavailability of cyclosporin. Monitoring of cyclosporin concentrations may be necessary.

*Monoamine Oxidase Inhibitors
Metoclopramide should be used cautiously, if at all in patients receiving monoamine oxidase inhibitors.

*Anticholinergic Drugs and Opioid Analgesics
Anticholinergic drugs and narcotic analgesics may antagonise the effects of metoclopramide on gastrointestinal motility.

No significant interaction
The following drugs have been demonstrated to be unaffected by concomitant administration of metoclopramide: atenolol, propranolol and TheoDur™ (slow release theophylline).

Suxamethonium
When metoclopramide is given concurrently with suxamethonium *or mivacurium the recovery time is prolonged.

Alcohol
Metoclopramide has been shown to significantly increase the absorption of alcohol.

CNS depressants and drugs that can cause extrapyramidal effects
CNS depressants *such as sedatives, hypnotics, narcotics, tranquillizers or anaesthetics* and drugs that can cause extrapyramidal effects should be used cautiously with metoclopramide since the adverse effects may be additive.

Laboratory tests
Metoclopramide increases serum prolactin acutely after each dose with a gradual return to normal by 6 to 12 hours.

ADVERSE REACTIONS

More common (>1%)
Restlessness, drowsiness, fatigue and lethargy occur in approximately 10% of patients and are the most common adverse reactions to metoclopramide.

Central nervous system: extrapyramidal symptoms are not uncommon during metoclopramide therapy and about 1% of patients treated have true dystonic reactions. High dose intravenous treatment with metoclopramide can produce acute reversible extrapyramidal symptoms in 2 to 30% of patients. Extrapyramidal symptoms occur most frequently in children and consist of trismus, torticollis, facial spasms, opisthotonos, oculogyric crisis and dysphagia.

They usually occur within 36 hours of therapy and subside within 24 hours of withdrawal of treatment. Most patients respond to anticholinergic agents such as benztropine or diazepam.
Patients with AIDS (acquired immunodeficiency syndrome) may have an increased incidence of extrapyramidal reactions.

**Less common (<1%)**

**Blood:** agranulocytosis, and methaemoglobinaemia (following overdose), have been reported in individual patients.

**Cardiovascular:** oedema, palpitations, irregular heart beats, *atrial fibrillation*, **ventricular fibrillation** (bradycardia, heart block and supraventricular tachycardia) have occurred infrequently.

Hypertensive crisis has been precipitated by metoclopramide. Metoclopramide may also induce transient hypotension of varying severity.

**Central Nervous System:** choreiform movements, dizziness, mania, depression, akathisia, agitation, *anxiety, insomnia, headache, neuroleptic malignant syndrome, delirium, severe dysphoria, obsessive rumination.*

Tardive dyskinesia has been reported in patients who have taken metoclopramide for prolonged (>1 year) periods of time.

Parkinson symptoms have been reported in patients receiving chronic metoclopramide therapy.

**Endocrine:** galactorrhoea, breast enlargement, porphyria, hyperthermia and neuroleptic malignant syndrome have all been reported in association with metoclopramide therapy.

**Gastrointestinal:** constipation, diarrhoea, taste disorders, *nausea.*

**Respiratory:** respiratory failure, secondary to dystonic reaction, acute asthmatic symptoms of wheezing and dyspnoea.

**Skin:** urticaria, maculopapular rash.

**Other:** urinary *frequency and incontinence, sexual dysfunction, priapism, muscle spasm.* *There have been isolated reports of blood disorders. Methaemoglobinaemia, particularly following overdose in neonates, has also occurred in patients receiving the drug. Agranulocytosis and hyperthermia have also been observed.*
**DOSAGE AND ADMINISTRATION**

The dosage recommendations given below 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 the nausea and vomiting.

**Maximum daily dose:** This should not exceed 0.5 mg/kg bodyweight, especially for children and young adults, when given by injection. However, when given diluted by intravenous infusion, a maximum of 10 mg/kg bodyweight may be given in any 24 hour period.

**Medical indications**

**Adults ≥ 20 years:** 10 mg three times a day, by intramuscular or slow (1 to 2 minutes) intravenous injection.

**Young adults 15 to 19 years:** 5 to 10 mg three times a day, starting at the lower dose, by intramuscular or slow (1 to 2 minutes) intravenous injection.

**Children**

To be given by intramuscular or slow (1 to 2 minutes) intravenous injection.

- **5 to 14 years:** 2.5 to 5 mg three times a day
- **3 to 5 years:** 2 mg two or three times a day
- **1 to 3 years:** 1 mg two or three times a day
- **under 1 year:** 1 mg twice daily.

**Treatment of nausea and vomiting due to cytotoxic drug therapy**

Up to 2 mg/kg bodyweight may be given diluted by intravenous infusion. The dose should be adjusted according to the dose of cytotoxic drug used and its propensity to cause emesis.

The initial dose should be given prior to commencement of cytotoxic therapy. Each dose should be added to at least 50 mL of a suitable diluent (see **COMPATIBILITIES**) and infused over at least 15 minutes. Dosage may be repeated at two hourly intervals up to a maximum of 10 mg/kg bodyweight in any 24 hours.

**Aid to gastrointestinal intubation**

A single dose of metoclopramide may be given 5 to 10 minutes before the examination. If the patient is lightly built the dose should be reduced.

- **Adults ≥ 20 years:** 10 to 20 mg
- **Young adults 15 to 19 years:** 10 mg
- **Children**
  - **9 to 14 years:** 5 mg
  - **5 to 9 years:** 2.5 mg
  - **3 to 5 years:** 2 mg
  - **under 3 years:** 1 mg

**Impaired renal and hepatic function**

Clearance of metoclopramide is likely to be reduced in patients with clinically significant degrees of renal or hepatic impairment. The doses given above should be halved in these patients, with subsequent dose adjustment being made as the individual response has been determined.
OVERDOSAGE

Symptoms
The most frequently reported adverse reactions to an overdose of metoclopramide are *drowsiness, disorientation and extrapyramidal symptoms. *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.

Management
Close observation of the patient, in addition to gastric emptying and supportive measures are required. Extrapyramidal reactions have been successfully controlled by antiparkinson and antihistamine/anticholinergic drugs such as diphenhydramine hydrochloride.

COMPATIBILITIES

Cytotoxic drugs:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Compatibility Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin sulfate</td>
<td>3 units/mL with metoclopramide hydrochloride 5 mg/mL visually compatible when injected sequentially into Y-site without flushing the Y-side arm between injections.</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>1 mg/mL with 5 mg/mL metoclopramide hydrochloride visually compatible when injected sequentially into Y-site without flushing the Y-side arm between injections.</td>
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<tr>
<td>Cyclophosphamide</td>
<td>20 mg/mL with metoclopramide hydrochloride 5 mg/mL visually compatible when injected sequentially into Y-site without flushing the Y-side arm between injections.</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>50 mg/mL with metoclopramide hydrochloride 5 mg/mL visually compatible when injected sequentially into Y-site without flushing the Y-side arm between injections.</td>
</tr>
<tr>
<td>Vinblastine sulfate</td>
<td>1 mg/mL with metoclopramide hydrochloride 5 mg/mL visually compatible when injected sequentially into Y-site without flushing the Y-side arm between injections.</td>
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</tbody>
</table>

Narcotic analgesics:

<table>
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</thead>
<tbody>
<tr>
<td>Morphine sulfate</td>
<td>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.</td>
</tr>
<tr>
<td>Pethidine HCl</td>
<td>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.</td>
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**Intravenous fluids:**
No preservative is included in the formulation of metoclopramide injection BP. 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.

Metoclopramide injection BP 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.

Further information on the compatibility of metoclopramide hydrochloride may be obtained from standard texts or the manufacturer.

**PRESENTATIONS**

Metoclopramide injections 5 mg/mL: 2 mL Polyamp® (polyethylene)
2 mL prefilled syringe

**SHELF-LIFE AND STORAGE**

Protect from light.
Polyamp:18 months when stored below 25°C
Prefilled syringe:18 months when stored below 25°C.

**NAME AND ADDRESS OF THE SPONSOR**

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road, North Ryde  NSW  2113 Australia

Polyamp and TheoDur are trade marks of the AstraZeneca group of companies

Date of TGA approval letter  18 May 1995
Date of Safety Related Notification  27 June 2003
* Denotes changes of clinical significance