

Metoperan Solution for Injection 5mg/mL

Metoclopramide Hydrochloride Monohydrate

Product Description

Description (before and after dilution): A colorless, clear liquid, free from visible particles.
Compatible diluents: Sodium Chloride Infusion (0.9% w/v) and Dextrose Infusion (5% w/v).

Composition

Each 2 mL injection ampoule contains 10 mg Metoclopramide Hydrochloride. This preparation also contains 20 mg Benzyl Alcohol as preservative and 0.5 mg Sodium Bisulfite as antioxidant.

Pharmacodynamics

The action of metoclopramide is closely associated with parasympathetic nervous control of the upper gastro-intestinal tract, where it has the effect of encouraging normal peristaltic action. This provides for a fundamental approach to the control of those conditions where disturbed gastro-intestinal motility is a common underlying factor. Metoclopramide stimulates activity of the upper gastro-intestinal tract and restores normal co-ordination and tone. Gastric emptying is accelerated and the resting tone of the gastroesophageal sphincter is increased. Metoclopramide is a dopamine-receptor antagonist with a direct anti-emetic effect on the medullary chemoreceptor trigger zone.

Pharmacokinetics

Absorption:

Metoclopramide is rapidly absorbed from the gastrointestinal tract and undergoes variable first-pass metabolism in the liver.

Biotransformation and Elimination:

Metoclopramide is metabolised in the liver and the predominant route of elimination of metoclopramide and its metabolites is via the kidney. It crosses the placenta and is excreted in breast milk. The elimination half-life is about 6 hours.

Renal impairment:

The clearance of metoclopramide is reduced by up to 70% in patients with severe renal impairment, while the plasma elimination half-life is increased (approximately 10 hours for a creatinine clearance of 10-50 mL/minute and 15 hours for a creatinine clearance <10 mL/minute).

Hepatic impairment:

In patients with cirrhosis of the liver, accumulation of metoclopramide has been observed, associated with a 50% reduction in plasma clearance.

Indication

Adult population:

Metoclopramide is indicated for use in adults for:

- Prevention of post-operative nausea and vomiting,
- Symptomatic treatment of nausea and vomiting, including nausea and vomiting induced by migraine attacks,
- Prevention of radiotherapy induced nausea and vomiting.

Paediatric population:

Metoclopramide is indicated in children aged 1 to 18 years for:

- Prevention of delayed Chemotherapy induced nausea and vomiting as a second-line option,
- Prevention of postoperative nausea and vomiting as a second-line option.

Recommended Dose and Administration

The solution can be administered by the intravenous or intramuscular route. The intravenous doses must be administered as a slow bolus (for at least 3 minutes).

All indications (adults)

A single 10 mg dose is recommended for the prevention of postoperative nausea and vomiting. The recommended dose for the symptomatic treatment of nausea and vomiting, including nausea and vomiting induced by migraine attacks and for the prevention of radiotherapy induced nausea and vomiting is 10 mg per dose, 1 to 3 times daily. The maximum recommended daily dose is 30 mg or 0.5 mg/kg.

Treatment duration when administering by injection should be as short as possible and a switch to administration via oral or rectal route should be instituted as quickly as possible.

All indications (children from 1 to 18 years of age)

The recommended dosage is 0.1 to 0.15 mg/kg, 1 to 3 times daily, by intravenous route. The maximum daily dose is 0.5 mg/kg.

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

For the prevention of delayed chemotherapy-induced nausea and vomiting, the maximum treatment duration is 5 days.

For the prevention of postoperative nausea and vomiting, the maximum treatment duration is 48 hours.

Frequency of administration: A minimum interval of 6 hours between two administrations is to be respected, even if vomiting or rejection of the dose occurs.

Special populations

Elderly subjects: In elderly subjects, a dose reduction should be considered, based on kidney and liver function, and overall frailty.

Kidney failure: In patients with end-stage kidney failure (creatinine clearances 15 ml/min), the daily dose should be reduced by 75%. In patients with moderate to severe kidney failure (creatinine clearance between 15 and 60ml/min), the dose should be reduced by 50%.

Liver failure: In patients with severe liver failure, the dose should be reduced by 50%.

Other pharmaceutical forms may be more suitable for these patient populations.

Pediatric population

Metoclopramide is contraindicated in children aged less than one year.

Total daily dose of metoclopramide, especially for children and young adults, should not normally exceed 0.5mg/kg body weight.

Mode of administration

Slow Intravenous or Intramuscular route.

Incompatibilities

Any dilutions of Metoclopramide 5 mg/ml Injection should be protected from light during infusion. Degradation is indicated by a yellow discoloration.

Such solution must not be used.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed
- Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk
- Confirmed or suspected pheochromocytoma, due to the risk of severe hypertension episodes
- History of neuroleptic or metoclopramide-induced tardive dyskinesia
- Epilepsy (increased crises frequency and intensity)
- Parkinson's disease
- Combination with levodopa or dopaminergic agonists
- Known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome-b5 deficiency
- Use in children less than 1 year of age

Warnings and Precautions

- Avoid doses exceeding 0.5mg/kg/day.

- Extrapyramidal effects, especially dystonic reaction of metoclopramide are more likely to occur in children shortly after initiation of therapy, and usually with doses higher than 0.5mg per kg of body weight per day.

Special Warnings and Precautions for Use

Neurological Disorders

Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions generally occur at the beginning of the treatment, and can occur after a single dose. If extrapyramidal symptoms occur, metoclopramide should be discontinued immediately. These effects are generally completely reversible after treatment discontinuation, however, symptomatic treatment may be required (benzodiazepines in children and/or anticholinergic antiparkinsonian medicinal products in adults).

An interval of at least six hours should be respected between each dose even if vomiting or rejection of the dose occurs, in order to avoid overdose.

Long-term treatment with metoclopramide may cause potentially irreversible tardive dyskinesia particularly in elderly subjects. Treatment should not exceed 3 months because of the risk of tardive dyskinesia. Treatment must be discontinued if clinical signs of tardive dyskinesia occur.

Neuroleptic malignant syndrome has been described with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy. Metoclopramide must be discontinued if symptoms of neuroleptic malignant syndrome develop, and appropriate treatment should be initiated.

Particular caution should be exercised in patients with underlying neurological conditions and in patients being treated with other centrally-acting drugs.

Symptoms of Parkinson's disease may also be exacerbated by metoclopramide.

Methaemoglobinaemia

Methaemoglobinaemia which could be related to NADH cytochrome b5 reductase deficiency, has been reported. If this occurs, treatment must immediately and permanently discontinued and appropriate measures initiated (such as treatment with methylene blue).

Cardiac Disorders

Serious cardiovascular undesirable effects including cases of severe bradycardia, circulatory collapse, cardiac arrest and QT prolongation has been reported during administration of metoclopramide by injection, particularly via the intravenous route.

Particular caution should be exercised when administering metoclopramide, particularly via the intravenous route, in elderly subjects, patients with cardiac conduction disorders (including QT prolongation), patients with electrolyte imbalance, bradycardia and patients taking other drugs known to prolong QT interval.

The intravenous injection must be given as a slow bolus (at least 3 minutes duration) in order to reduce the risk of undesirable effects (e.g. hypotension, akathisia).

Kidney or liver failure

In patients with kidney or severe liver failure, a dose reduction is recommended.

As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age.
Not to be used in neonates

Interactions with Other Medicaments

Contraindicated combination

Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism.

Combination to be avoided

Alcohol potentiates the sedative effect of metoclopramide.

Combination to be taken into account

Due to the effect of metoclopramide, the absorption of certain drugs may be modified.

Anticholinergics and morphine derivatives

Anticholinergics and morphine derivatives may both have a mutual antagonism with metoclopramide on the digestive tract motility.

Central nervous system depressants (morphine derivatives, anxiolytics, sedative H1 antihistamines, sedative antidepressants, barbiturates, clonidine and related).

Sedative effects of Central Nervous System depressants and metoclopramide are potentiated.

Neuroleptics

Metoclopramide may have an additive effect with other neuroleptics on the occurrence of extrapyramidal disorders.

Serotonergic drugs

The use of metoclopramide with serotonergic drugs such as SSRIs may increase the risk of serotonin syndrome.

Digoxin

Metoclopramide may decrease digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.

Cyclosporine

Metoclopramide increases cyclosporine bioavailability (Cmax by 46% and exposure by 22%). Careful monitoring of cyclosporine plasma concentration is required. The clinical consequence is uncertain.

Mivacurium and suxamethonium

Metoclopramide injection may prolong the duration of neuromuscular block (through inhibition of plasma cholinesterase).

Strong CYP2D6 inhibitors

Metoclopramide exposure levels are increased when co-administered with strong CYP2D6 inhibitors such as fluoxetine and paroxetine. Although the clinical significance is uncertain, patients should be monitored for adverse reactions.

The effects of certain other drugs with potential central stimulant effects, e.g. monoamine oxidase inhibitors and sympathomimetics, may be modified when prescribed with metoclopramide and their dosage may need to be adjusted accordingly.

Aspirin, paracetamol

The effect of metoclopramide on gastric motility may modify the absorption of other concurrently administered oral drugs from the gastro-intestinal tract either by diminishing absorption from the stomach or by enhancing the absorption from the small intestine (e.g. the effects of paracetamol and aspirin are enhanced).

Atovaquone

Metoclopramide injection may reduce plasma concentrations of atovaquone.

Pregnancy and Lactation

Pregnancy period:

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative toxicity nor foetotoxicity. Metoclopramide can be used during pregnancy if clinically needed. Due to pharmacological properties (as other neuroleptics), in case of metoclopramide administration at the end of pregnancy, extrapyramidal syndrome in the newborn cannot be excluded. Metoclopramide should be avoided at the end of pregnancy. If metoclopramide is used, neonatal monitoring should be undertaken.

Lactation period:

Metoclopramide is excreted in breast milk at a low level. Adverse reactions in the breast-fed baby cannot be excluded. Therefore metoclopramide is not recommended during breastfeeding. Discontinuation of metoclopramide in breastfeeding women should be considered.

Side Effects

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders		
	Not known	Methaemoglobinaemia, which could be related to NADH cytochrome b5 reductase deficiency, particularly in neonates Sulphaemoglobinaemia, mainly with concomitant administration of high doses of sulphur-releasing medicinal products
Cardiac disorders		
	Uncommon	Bradycardia, particularly with intravenous formulation
	Not known	Cardiac arrest, occurring shortly after injectable use, and which can be subsequent to bradycardia; Atrioventricular block, Sinus arrest particularly with intravenous formulation; Electrocardiogram QT prolonged; Torsade de Pointes
Endocrine disorders*		
	Uncommon	Amenorrhoea, Hyperprolactinaemia,
	Rare	Galactorrhoea
	Not known	Gynaecomastia
Gastrointestinal disorders		
	Common	Diarrhoea
General disorders and administration site conditions		
	Common	Asthenia
	Not Known	Injection site inflammation and local phlebitis
Immune system disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock) particularly with intravenous formulation
Nervous system disorders		
	Very common	Somnolence
	Common	Extrapyramidal disorders (particularly in children and young adults and/or when the recommended dose is exceeded, even following administration of a single dose of the drug), Parkinsonism, Akathisia
	Uncommon	Dystonia (including visual disturbances and oculogyric crisis), Dyskinesia, Depressed level of consciousness
	Rare	Convulsion especially in epileptic patients
	Not known	Tardive dyskinesia which may be persistent, during or after prolonged treatment, particularly in elderly patients, Neuroleptic malignant syndrome
Psychiatric disorders		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional state
Vascular disorder		
	Common	Hypotension, particularly with intravenous formulation
	Not known	Shock, syncope after injectable use. Acute hypertension in patients with pheochromocytoma. Transient increase in blood pressure
Skin disorder		
	Not known	Skin reactions such as rash, pruritus, angioedema and urticaria

*Endocrine disorders during prolonged treatment in relation with hyperprolactinaemia (amenorrhoea, galactorrhoea, gynaecomastia).

The following reactions, sometimes associated, occur more frequently when high doses are used:

- Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonian syndrome, akathisia, even following administration of a single dose of the medicinal product, particularly in children and young adults.

- Drowsiness, decreased level of consciousness, confusion, hallucination.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Symptoms and Treatment of Overdose

Symptoms

Extrapyramidal disorders, drowsiness, a decreased level of consciousness, confusion, hallucination and cardio-respiratory arrest may occur.

Treatment

In case of extrapyramidal symptoms related or not to overdose, the treatment is only symptomatic (benzodiazepines in children and/or anticholinergic anti-parkinsonian medicinal products in adults).

A symptomatic treatment and a continuous monitoring of the cardiovascular and respiratory functions should be carried out according to clinical status.

Route of Administration:

The solution can be administered intravenously or intramuscularly.

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

Storage Conditions

Do not store above 30°C. Keep the ampoules in the outer carton in order to protect from light. Please use immediately after opening.

Shelf-Life

48 months

Dosage Forms and Packaging Available

2 mL injection ampoule - Box of 10 ampoules.

Registration Number

Metoperan Solution for Injection 5 mg/mL – MAL24056069AZ

Manufacturer

SIU GUAN CHEMICAL IND. CO., LTD.

No. 128, Shinmin Road, Hunei Village, West District, Chiayi City, TAIWAN

Product Registration Holder

Averroes Pharmaceuticals Sdn. Bhd.

03-08-01 & 03-09-01, Block 3,

Presint Alami, Worldwide Business Center II,

Persiaran Akuatik, Seksyen 13

40100 Shah Alam, Selangor

Malaysia

Tel : +603 5511 1433

Fax: +603 5511 1431

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