

Patient Information Leaflet

Read all of this patient information leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Metoclopramide-hameln 5 mg/ml Injection

PRODUCT DESCRIPTION

Clear, colourless solution

COMPOSITION

Each 1 ml contains:

Metoclopramide hydrochloride 1 H ₂ O	5.268 mg
equivalent to metoclopramide HCl	5.000 mg

1 ampoule with 2 ml solution for injection contains

Metoclopramide hydrochloride 1 H ₂ O	10.536 mg
equivalent to metoclopramide HCl	10.000 mg

List of excipients:

Sodium chloride, citric acid monohydrate, sodium citrate dihydrate, water for injections, 1 N sodium hydroxide solution or 1 N hydrochloric acid (for pH adjustment)

1 ampoule of 2 ml solution for injection contains 6.37 mg sodium (= 0.28 mval sodium).

PROPERTIES

Pharmacodynamic properties:

Pharmacotherapeutic group: Drugs for functional gastrointestinal disorders, Propulsives.

ATC code: A03FA01

Metoclopramide is a central dopamine antagonist. In addition it shows peripheral cholinergic activity. Two principal actions may be distinguished: (1) an antiemetic effect; (2) accelerated gastric emptying and small-intestinal transit.

The antiemetic effect is mediated by a central action on the brainstem (chemoreceptor trigger zone of the vomiting centre), probably via inhibition of dopaminergic neurones. The increased motility is also partly directed by higher centres, but a peripheral mechanism of action also operates via activation of postganglionic cholinergic receptors; inhibition of dopaminergic receptors in the stomach and small bowel may also play a part.

On prolonged administration, the lack of dopaminergic inhibition of prolactin secretion may lead to a rise in the serum prolactin concentration.

Pharmacokinetic properties:

Absorption:

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

After intramuscular administration, the relative bioavailability compared to intravenous application is 60 to 100 %. Peak plasma levels are reached within 0.5 to 2 hours.

Distribution:

The distribution volume is 2-3 l/kg; 13-22% is bound to plasma proteins.

Biotransformation:

Metoclopramide is metabolised in the liver.

Elimination:

The predominant route of elimination of metoclopramide and its metabolites is via the kidney, both in unchanged form and in sulfate or glucuronide conjugate form. The main metabolite is N-4 sulfur conjugate. It crosses the placenta and is excreted in breast milk. The plasma elimination half-life is about 5 to 6 hours, regardless of the route of administration.

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.

INDICATIONS

Adult population:

Metoclopramide-hameln 5 mg/ml Injection, 2 ml 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 chemotherapy- or radiotherapy-induced nausea and vomiting

Pediatric population:

Metoclopramide-hameln 5 mg/ml Injection, 2 ml 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 post-operative nausea and vomiting as a second-line option

DOSE AND ADMINISTRATION

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

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 post-operative 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.

The maximum recommended treatment duration is 5 days.

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.

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

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

For the prevention of post-operative 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 clearance ≤ 15 ml/min), the daily dose should be reduced by 75%.

In patients with moderate to severe kidney failure (creatinine clearance between 15 and 60 ml/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.

Compatibility:

Metoclopramide Injection has been shown to be compatible with the following infusion solutions:

- Sodium chloride Intravenous infusion BP (0.9% w/v)
- Dextrose Intravenous Infusion BP (5% w/v)
- Sodium chloride and Dextrose Intravenous Infusion BP (Sodium chloride 0.18% w/v and Dextrose 4% w/v)
- Compound sodium lactate Intravenous Infusion BP (Ringer lactate solution, Hartman's solution)
- 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

Metoclopramide-hameln 5 mg/ml Injection must not be used in the following situations:

- 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 due to an increased risk of extrapyramidal disorders
- Metoclopramide 5 mg/ml Injection should not be used during the first three to four days following operations such as pyloroplasty or gut anastomosis as vigorous muscular contractions may not help healing
- Metoclopramide should not be used during breast-feeding

WARNING AND PRECAUTIONS

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 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 and with metoclopramide monotherapy. Metoclopramide must be immediately discontinued if symptoms of neuroleptic malignant syndrome develop, and appropriate treatment should be initiated.

Particular caution should be exercised in patients with underlying neurological disorders, and in patients receiving other centrally-acting drugs.

Metoclopramide should be used with caution in patients with hypertension, since there is limited evidence that the drug may increase circulating catecholamines in such patients.

Because metoclopramide can stimulate gastro-intestinal mobility, the drug theoretically could produce increased pressure on the suture lines following gastro-intestinal anastomosis or closure.

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

Methemoglobinemia

Methemoglobinemia, which could be related to NADH-cytochrome b5 reductase deficiency, has been reported. If this occurs, treatment must be 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 have 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 (e.g., class IA and III antiarrhythmic drugs, tricyclic antidepressants, macrolides, antipsychotics (see section *Side Effects*)).

The intravenous injection must be given as a slow bolus (of 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 failure or severe liver failure, a dose reduction is recommended.

Metoclopramide may cause elevation of serum prolactin levels.

Care should be exercised when using Metoclopramide 5 mg/ml Injection in patients with a history of atopy (including asthma) or porphyria.

Special care should be taken when administering Metoclopramide 5 mg/ml Injection intravenously to patients with "sick sinus syndrome" or other cardiac conduction disturbances.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule (2 ml), that is to say essentially 'sodium-free'.

DRUG INTERACTIONS

Contraindicated combination

Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism (see section CONTRAINDICATIONS).

Combination to be avoided

Alcohol potentiates the sedative effect of metoclopramide.

Combination to be taken into account

Due to the prokinetic 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 (C_{max} 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.

Rifampicin

In a published study conducted in 12 healthy volunteers, the administration of 600 mg of rifampicin for 6 days led to reduced plasma metoclopramide exposure (AUC area under the curve) and maximum concentration (C_{max}) by 68% and 35%, respectively. Although the clinical significance is uncertain when metoclopramide is combined with rifampicin, or with other strong inducers (e.g. carbamazepine, phenobarbital, phenytoin), patients should be monitored for a possible lack of anti-emetic activity

Fertility, pregnancy and lactation

Pregnancy

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.

Breastfeeding

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.

Effects on ability to drive and use machines

Metoclopramide has moderate influence on the ability to drive and use machines.

Metoclopramide may cause drowsiness, dizziness, dyskinesia and dystonias which could affect the vision and also interfere with the ability to drive and operate machinery.

SIDE EFFECTS

Adverse reactions listed by System Organ Class. Frequencies are defined using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10000$, $< 1/1000$), very rare ($< 1/10000$), not known (cannot be estimated from the available data).

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 (see section <i>Warnings and Precautions</i>) Sulfhaemoglobinaemia, mainly with concomitant administration of high doses of sulfur-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 (see section <i>Warnings and Precautions</i>); 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) (see section <i>Warnings and Precautions</i>), 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 (see section <i>Warnings and Precautions</i>), Neuroleptic malignant syndrome (see section <i>Warnings and Precautions</i>)
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 phaeochromocytoma (see section <i>Contraindications</i>). 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 (see section *Warnings and Precautions*).
- 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.

Healthcare professionals are asked to report any suspected adverse reactions via the national system.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

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

Management

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.

PACKING OR PACK SIZES

Box of 5 or 10 ampoules with 2 ml solution for injection.

STORAGE CONDITIONS

Do not store above 30°C. Protect from light.

Keep the ampoules in the outer carton in order to protect from light.

Keep out of reach of children.

Jauhi daripada kanak-kanak.

Shelf life

Please refer to the outer box label.

Manufacturer

Mefar İlaç Sanayii A.Ş.

Ramazanoğlu Mah. Ensar Cad. No: 20

34906 Kurtköy/ Pendik/ İstanbul

Türkiye

Date of revision:

07/2024