Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Metoclopramide 5mg/ml Injection BP

2. Qualitative and quantitative composition
Each ml contains Metoclopramide Hydrochloride 5 mg

(anhydrous)

Excipients with known effect
Each injection contains Propylene Glycol BP.
For the full list of excipients, see section 6. 1

3. Pharmaceutical form
Clear colourless solution filled in amber colour glass ampoule.

4. Clinical particulars

4.1 Therapeutic indications

Paediatric population:

Metoclopramide 5 mg/ml Injection is indicated in children (1 – 18 years) for:

- Prevention of delayed chemotherapy induced nausea and vomiting (CINV) as a second line option
- Treatment of established post-operative nausea and vomiting (PONV) as a second line option.

For other indications, the use in the paediatric population is not recommended.

Adult population:

Metoclopramide 5 mg/ml Injection is indicated in adults for**:**

- Prevention of post-operative nausea and vomiting (PONV)
- Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting
- Prevention of radiotherapy induced nausea and vomiting (RINV)

4.2 Posology and method of administration

Posology

The solution can be administered intravenously or intramuscularly.

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

All indications (pediatric patients aged 1-18 years)

The recommended dose is 0.1 to 0.15 mg/kg body weight, repeated up to three times daily by intravenous route. The maximum dose in 24 hours is 0.5 mg/kg body weight.
A minimal interval of 6 hours between two administrations is to be respected, even in case of vomiting or rejection of the dose.

Table 1: Dosing table

Age	Body Weight	Dose	Frequency
1-3 years	10-14kg	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 maximum treatment duration is 48 hours for treatment of established post-operative nausea and vomiting (PONV).
The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).
All indications (adult patients)

For prevention of PONV a single dose of 10mg is recommended. For the symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting and for the prevention of radiotherapy induced nausea and vomiting (RINV): the recommended single dose is 10 mg, repeated up to three times daily.
The maximum recommended daily dose is 30 mg or 0.5mg/kg body weight.

The injectable treatment duration should be as short as possible and transfer to oral or rectal treatment should be made as soon as possible.
The maximum recommended treatment duration is 5 days.

Special population Elderly

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

Renal impairment

In patients with end stage renal disease (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%.

Hepatic impairment

In patients with severe hepatic impairment, the dose should be reduced by 50%.

Paediatric population

Metoclopramide is contraindicated in children aged less than 1 year

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Gastrointestinal haemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk.

Confirmed or suspected phaeochromocytoma, 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.

4.4 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 occur usually at the beginning of the treatment and can occur after a single administration. Metoclopramide should be discontinued immediately in the event of extrapyramidal symptoms. These effects are generally completely reversible after treatment discontinuation, but may require a symptomatic treatment (benzodiazepines in children and/or anticholinergic anti-Parkinsonian medicinal products in adults).
The time interval of at least 6 hours should be respected between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose. Prolonged treatment with metoclopramide may cause tardive dyskinesia, potentially irreversible, especially in the elderly. Treatment should not exceed 3 months because of the risk of tardive dyskinesia. Treatment must be discontinued if clinical signs of tardive dyskinesia appear.
Neuroleptic malignant syndrome has been reported with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy. Metoclopramide should be discontinued immediately in the event of symptoms of neuroleptic malignant syndrome and appropriate treatment should be initiated.
Special care should be exercised in patients with underlying neurological conditions and in patients being treated with 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.

<u>Methaemoglobinaemia</u>

Methaemoglobinaemia which could be related to NADH cytochrome b5 reductase deficiency has been reported. In such cases, metoclopramide should be immediately and permanently discontinued and appropriate measures initiated (such as treatment with methylene blue).

Cardiac Disorders

There have been reports of serious cardiovascular undesirable effects including cases of circulatory collapse, severe bradycardia, cardiac arrest and QT prolongation following administration of metoclopramide by injection, particularly via the intravenous route. Special care should be taken when administering metoclopramide, particularly via the intravenous route to the elderly population, to patients with cardiac conduction disturbances (including QT prolongation), patients with uncorrected electrolyte imbalance, bradycardia and those taking other drugs known to prolong QT interval.

Intravenous doses should be administered as a slow bolus (at least over 3 minutes) in order to reduce the risk of adverse effects (e.g. hypotension, akathisia).

Renal and Hepatic Impairment

In patients with renal impairment or with severe hepatic impairment, 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.

4.5 Interaction with other medicinal products and other forms of Interactions

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 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 (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.

4.6 Pregnancy and Lactation

Pregnancy

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicates neither 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

4.7 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

4.8 Undesirable effects

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

Table 2: Tabulated adverse reactions

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. Sulfhaemoglobinaemia, 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 administr ıtion site conditions		
	Common	Asthenia
	Not Known	Injection site inflammation and local phlebitis
Immune system disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including shock) anaphylactic 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 phaeochromocytoma. 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, and hallucination.

4.9 Overdose

Symptoms

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Agents stimulating gastro-intestinal motility.

ATC Code: A03FA01

Mechanism of action

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 coordination and tone. Gastric emptying is accelerated and the resting tone of the gastrooesophageal sphincter is increased. Metoclopramide is a dopamine-receptor antagonist with a direct anti-emetic effect on the medullary chemoreceptor trigger zone.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

No additional data available.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium Metabisulfite BP

Propylene Glycol BP

Phenol BP

Sodium Di-Hydrogen Orthophosphate Dihydrate BP

Water for injections BP

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

6.2 Shelf-Life

36 Months

6.3 Special Precautions for storage

Store at a temperature not exceeding 30°C. Protect from light

6.4 Nature and Content of container

10x2ml amber color glass ampoules placed in a plastic tray, such tray packed in a carton, along with pack insert.

6.5 Special precautions for disposal and other handling

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)

7. Marketing Authorization Holder

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8. Marketing Authorization Number

9. Date of first authorization/renewal of the authorization
20/1/2025

10. Date of revision of the text
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