Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metoclopramide 5mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2ml contains metoclopramide hydrochloride equivalent to 10mg of anhydrous metoclopramide hydrochloride.

Excipient(s) with known effect
Sodium Metabisulphite (E223) - 2 mg/2 ml (i.e. 1mg/ml)
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection
Clear colourless sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metoclopramide 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).

Paediatric population:
Metoclopramide is indicated in children (aged 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

Metoclopramide should not be used in children younger than 1 year as there are insufficient data regarding efficacy and safety of the product in this population.

4.2 Posology and method of administration

Posology:

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).

Adult population

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.

All indications (paediatric 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.

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 60kg	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).

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% (see section 5.2).

Hepatic impairment:

In patients with severe hepatic impairment, the dose should be reduced by 50% (see section 5.2).

Paediatric population
Metoclopramide is contraindicated in children aged less than 1 year (see section 4.3).

Method of administration:
A minimal interval of 6 hours between two administrations is to be respected, even in case of vomiting or rejection of the dose (see section 4.4).

4.3 Contraindications

-Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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 (see section 4.5)
- 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 (see section 4.4)

4.4 Special warnings and precautions for use

Neurological disorder

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 specified in the section 4.2 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 (see section 4.8). 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 (see section 4.8).
Metoclopramide should be discontinued immediately in the event of symptoms of neuroleptic malignant syndrome and appropriate treatment should be initiated.
Metoclopramide 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.
Special care should be exercised in patients with underlying neurological conditions and in patients being treated with other centrally-acting drugs (see section 4.3)
Symptoms of Parkinson's disease may also be exacerbated by metoclopramide.

Methaemoglobinemia

Methemoglobinemia 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 (see section 4.8).

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).

Special care should be taken when administering to patients with "sick sinus syndrome" or other cardiac conduction disturbances.

Renal and Hepatic Impairment

In patients with renal impairment or with severe hepatic impairment, a dose reduction is recommended (see section 4.2).
If vomiting persists the patient should be reassessed to exclude the possibility of an underlying disorder e.g. cerebral irritation.

Metoclopramide may cause elevation of serum prolactin levels.

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

Important information on excipients sodium metabisulphite and sodium

• Metoclopramide contains sodium metabisulphite. Sodium metabisulphite may rarely cause severe hypersensitivity (allergic) reactions and bronchospasm (breathing difficulties).

• This medicinal product contains less than 1mmol sodium (23 mg) per dose, that is to say essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combination
Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism (see section 4.3).

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 have both a mutual antagonism with metoclopramide on the digestive tract motility.
The action of ' Metoclopramide ' on the gastrointestinal tract is antagonised by anticholinergics and opioid analgesics. The absorption of any concurrently administered oral medication may be modified by the effect of Metoclopramide on gastric motility. Drugs known to be affected in this way include aspirin and paracetamol.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicates no malformative toxicity nor feto/ neonatal toxicity of Metoclopramide hydrochloride. 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 newborn cannot be excluded. Metoclopramide should be avoided at the end of pregnancy. If metoclopramide is used, neonatal monitoring should be undertaken.

Breast-feeding

Metoclopramide is excreted in breast milk at 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.

Fertility

No data available.

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 or 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 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), 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 4.4); Sulfhaemoglobinaemia, mainly with concomitant administration of high doses of sulphur-releasing medicinal products
Immune system disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock particularly with intravenous formulation, Skin reactions such as rashes, urticaria, pruritus and angioedema
Endocrine disorders*		
	Uncommon	Amenorrhoea, Hyperprolactinaemia,
	Rare	Galactorrhoea
	Not known	Gynaecomastia
Psychiatric disorders		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional state, restlessness, agitation.
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 4.4), 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 4.4), Neuroleptic malignant syndrome (see section 4.4), dizziness, drowsiness, tremor
Eye disorders		
	Not known	Visual disturbances
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 4.4); Atrioventricular block, Sinus arrest particularly with intravenous formulation; Electrocardiogram QT prolonged; Torsade de Pointes;
Vascular disorder		
	Common	Hypotension, particularly with intravenous formulation
	Not known	Shock, syncope after injectable use Acute hypertension in patients with phaeochromocytoma (see section 4.3), Transient increase in blood pressure
Respiratory, thoracic and mediastinal disorders		
	Not known	Dyspnoea
Gastrointestinal disorders		
	Common	Diarrhoea
General disorders and administration site conditions		
	Common	Asthenia
	Rare	anxiety
	Not known	Oedema

* 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 4.4).
- 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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms

Extrapyramidal disorders, drowsiness, 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 gastrointestinal tract, where it has the effect of encouraging normal peristaltic action. Metoclopramide is a benzamide derivative which acts peripherally to enhance cholinergic action at muscarinic synapses and in the central nervous system to antagonize dopamine. This provides for a fundamental approach to the control of those conditions where disturbed gastrointestinal motility is a common underlying factor.

5.2 Pharmacokinetic properties

Absorption
Absorption from the gastrointestinal tract is rapid.

Biotransformation
The drug undergoes significant first pass hepatic metabolism.

Elimination
It is excreted in the urine as unchanged drug and metabolites in both free and conjugated form. The drug is also excreted in breast milk.

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 further information other than that which is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Metabisulphite (E223)
Sodium Chloride
Water for Injections
Hydrochloric Acid
Sodium Hydroxide

6.2 Incompatibilities

Metoclopramide is reported to be incompatible with sodium bicarbonate, cephalothin sodium and other cephalosporins, and chloramphenicol. Do not mix with other drugs unless compatibility is known.

6.3 Shelf life

Unopened: 3 years.
The product should be used immediately after opening.

6.4 Special precautions for storage

Keep the ampoule in the original carton in order to protect from light.
Do not store above 25^{o}C.

6.5 Nature and contents of container

Clear glass one-point-cut (OPC) ampoules, glass type I Ph. Eur.
Pack size: 10 x 2ml ampoules.

6.6 Special precautions for disposal and other handling

For single use only
If only part used, discard the remaining solution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd
4045 Kingswood Road
Citywest Business Park
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0073/084/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 October 1984
Date of last renewal: 11 October 2009

10 DATE OF REVISION OF THE TEXT

September 2022