SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metoclopramide 5 mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 2 ml solution for Injection contains metoclopramide hydrochloride monohydrate equivalent to 10 mg of metoclopramide hydrochloride anhydrous.

Each ampoule of 10 ml solution for Injection contains metoclopramide hydrochloride monohydrate equivalent to 50 mg of metoclopramide hydrochloride anhydrous.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless, sterile solution.
Osmolality: between 250 mOsmol/L and 350 mOsmol/L.
pH between 3.00 and 5.00

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult population:
Metoclopramide 5 mg/ml Solution for 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).

Paediatric population
Metoclopramide 5 mg/ml Solution for Injection 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 postoperative nausea and vomiting (PONV) as a second line option.

4.2 Posology and method of administration

Due to the risk of severe cardiovascular reactions such as cardiac arrest, the use of the solution for injection is limited to situations where the necessary resuscitation equipment is available (see sections 4.4 and 4.8).

The solution can be administered intravenously or intramuscularly.
Intravenous doses should be administered as a slow bolus (over at least 3 minutes).

All indications (adult patients)
For prevention of PONV a single dose of 10 mg 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 0.5 mg/kg body weight.

The injectable treatment duration should be as short as possible and a switch to oral or rectal treatment should be made as soon as possible.

All indications (paediatric population 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 60 kg	10 mg	Up to 3 times daily

The maximum treatment duration is 48 hours for treatment of established postoperative nausea and vomiting (PONV).

The maximum treatment duration is 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).

Special patient groups

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

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 5 mg/ml Solution for Injection 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 of the dose (see section 4.4).

4.3 Contraindications

- Hypersensitivity to active substance or any of the excipients listed in section 6.1.
- Gastrointestinal haemorrhage, mechanical obstruction or gastrointestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk.
- Confirmed or suspected phaeochromocytoma associated with the risk of severe hypertension episodes.
- History of neuroleptic or metoclopramide-induced tardive dyskinesia.
- Epilepsy (increased crisis frequency and intensity).
- Parkinson's disease.
- Combination with levodopa or dopaminergic agonists (see section 4.5).
- Known history of methaemoglobinaemia with metoclopramide or 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 disorders
Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions usually occur 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 section 4.2 should be respected between each metoclopramide administration, even in case of vomiting of the dose, in order to avoid overdose.

Prolonged treatment with metoclopramide may cause tardive dyskinesia, which is 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.

Special care should be exercised in patients with underlying neurological conditions and in patients being treated with other drugs that act on the central nervous system (see section 4.3).

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. 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 4.2 and 4.8).

Special care should be taken when administering metoclopramide, particularly via the intravenous route to the elderly population, to patients with cardiac conduction disorders (including QT prolongation), patients with uncorrected electrolyte imbalance, bradycardia and those taking other drugs known to prolong QT interval (such as class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics (see section 4.8)).

Intravenous doses should be administered as a slow bolus (over at least 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 (see section 4.2).

Other precautions
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.

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

This medicinal product contains less than 1 mmol 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
Concomitant use of levodopa or dopaminergic agonists and metoclopramide is contraindicated due to 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 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 products) The 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.

Ciclosporin
Metoclopramide increases ciclosporin bioavailability (Cmax by 46% and exposure by 22%). Careful monitoring of ciclosporin plasma concentration is required. The clinical consequences are uncertain.

Mivacurium and suxamethonium
Metoclopramide 5 mg/ml Solution for 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 1,000 pregnancy outcomes) indicate no malformative nor feto-toxicity of metoclopramide. Metoclopramide can be used during pregnancy if clinically needed. Due to pharmacological properties (as with 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 human milk at low levels. Adverse reactions in the breastfed 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 5 mg/ml Solution for Injection may cause sleepiness, dizziness, dyskinesia and dystonia which could affect 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 (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable effects
Immune system disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock particularly with intravenous formulations)
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
Cardiac disorders		
	Uncommon	Bradycardia, particularly with intravenous formulations
	Not known	Cardiac arrest, occurring shortly after injectable use, and which can be subsequent to bradycardia (see section 4.2 and 4.4); 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
Nervous system disorders		
	Very common	sleepiness
	Common	Extrapyramidal disorders (particularly in children and young adults and/or when the recommended dose is exceeded, even

System Organ Class	Frequency	Undesirable effects
		following administration of a single dose of the medicinal product) (see section 4.4), Parkinsonism, akathisia
	Uncommon	Dystonia (including visual disturbances and oculogyric crisis), dyskinesia, depressed level 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)
Psychiatric disorders		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional state
	Not known	Suicidal ideation
Vascular disorders		
	Common	Hypotension, particularly with intravenous formulations
	Not known	Shock, syncope (fainting) after injectable use. Acute hypertension in patients with phaeochromocytoma (see section 4.3). Transient increase in blood pressure.

* Endocrine disorders during prolonged treatment in relation to 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, acathesia, even following administration of a single dose of the medicinal product, particularly in children and young adults (see section 4.4).
- Sleepiness, depressed level of consciousness, fuzzy thinking, 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 United KingdomYellow Card Scheme. Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

Extrapyramidal disorders, sleepiness, depressed level of consciousness, fuzzy thinking, 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).

Symptomatic treatment and continuous monitoring of cardiovascular and respiratory functions should be carried out according to clinical status.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives.

ATC code: A03F (A).

Metoclopramide is a substituted benzamide. It is used among other things for its anti-emetic properties. Its anti-emetic effect due to two central-acting mechanisms of action:

- antagonism of the dopaminergic D2 receptors in the chemoceptor trigger zone and in the vomiting centre of the medulla involved in apomorphine-induced vomiting;
- antagonism of the serotoninergic 5HT3 receptors and agonism of the 5HT4 receptors involved in chemotherapy-induced vomiting.

In addition to its central action, metoclopramide has a stimulatory effect on digestive motor activity through a peripheral mode of action. It has an anti-dopaminergic effect and potentiates the action of acetylcholine. This results in an accelerated gastric emptying and increase in the pressure of the lower oesophageal sphincter. Metoclopramide does not affect gastric secretion.

5.2 Pharmacokinetic properties

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

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

Metoclopramide is mainly excreted in the urine, both in unchanged form and in sulphate or glucuronide conjugate form. The main metabolite is N-4 sulphur conjugate.

The plasma elimination half-life is 5 to 6 hours, regardless of 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 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 indications of a safety risk in humans were found in laboratory animals. This is based on data from safety pharmacology studies, and data on repeated dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric Acid Monohydrate (E330)
Sodium citrate (E331)
Sodium chloride
Sodium hydroxide (E524) (for pH adjustment)
Hydrochloric acid (E507) (for pH adjustment)
Water for injection.

6.2 Incompatibilities

The medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Before Opening: 2 Years

Chemical and physical in-use stability has been demonstrated for 24 hrs at 25˚ C.

From a microbiology point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to used are the responsibility of the user and would normally not be longer than 24 hrs at 2 to 8˚ C, unless reconstitution has taken place in controlled and validated aseptic condition.

6.4 Special precautions for storage

Store ampoule in the original package in order to protect from light.
Do not store in the refrigerator or freezer
For storage conditions after first opening of the medicinal product, see section 6.3

6.5 Nature and contents of container

Type I clear glass ampoule of 2 ml fill volume and 10 mL fill volume.

Metoclopramide 5mg/ml Solution for Injection is available in glass ampoule containing 2 ml solution and 10 mL solution which are packed in blister and further packed in cardboard boxpack as below:

5 x 2 mL, 10 x 2 mL and 25 x 2 mL
5 x 10 mL and 10 x 10 mL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

If only part of an ampoule is used, discard the remaining solution.
After opening: from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Metoclopramide 5 mg/ml Solution for Injection is compatible with the following solutions for infusion for 24 hours:
1) 0.9 % Sodium Chloride Injection
2) 5% Dextrose Injection
3) 4% Dextrose in 0.18 % Sodium chloride
4) Ringer lactate solution

7. MARKETING AUTHORISATION HOLDER

Baxter Healthcare Limited
Caxton Way
Thetford, Norfolk IP24 3SE, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 00116/0694

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10 DATE OF REVISION OF THE TEXT

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