SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metoclopramide 5 mg/ml Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each 10 ml contains metoclopramide hydrochloride BP equivalent to 50 mg of anhydrous metoclopramide hydrochloride.

Each 20 ml contain metoclopramide hydrochloride BP equivalent to 100 mg of anhydrous metoclopramide hydrochloride.

3 PHARMACEUTICAL FORM

Sterile injection or infusion.

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

The solution can be administered intravenously or intramuscularly.

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

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.

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).

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% (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)

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 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 (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)
- 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 (see Section 4.6).

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 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.

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).

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.

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 4.8).

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 (e.g., class IA and III antiarrhythmic drugs, tricyclic antidepressants, macrolides, antipsychotics (see section 4.8)).

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 (see section 4.2).

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'.

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 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.

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 (Cmax) 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.

4.6 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.

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).

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 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 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
	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 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)
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 4.3). 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 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 the Yellow Card Scheme Website at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: Drugs for functional gastrointestinal disorders, Propulsives.
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 co-ordination 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

Abpsortion:

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.

5.3 Preclinical safety data

No further information other than that which is included in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Citric Acid Monohydrate
Sodium Citrate
Hydrochloric acid: for pH adjustment
Sodium hydroxide : for pH adjustment
Nitrogen
Water for Injections

6.2 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.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C.

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

6.5 Nature and contents of container

Type I clear glass ampoules 2 ml, 10 ml and 20 ml packed in cardboard cartons to contain 10 ampoules in each.

6.4 Special precautions for disposal and 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 AUTHORISATION HOLDER

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Nexus, Gloucester Business Park
Gloucester, GL3 4AG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 01502/0044

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