SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metoclopramide 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active constituents: metoclopramide hydrochloride 10.55* mg.
*10.55 mg equivalent to 10mg anhydrous metoclopramide hydrochloride
Excipients with known effect:
Each tablet contains 88.0 mg of Lactose. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White uncoated tablet. Side one embossed “a” and “M/10” on either side of breakline, intended for oral administration to human beings.
The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult population
Metoclopramide is indicated in adults for:

- Prevention of delayed chemotherapy induced nausea and vomiting (CINV)
- Prevention of radiotherapy induced nausea and vomiting (RINV).
- Symptomatic treatment of nausea and vomiting, including acute migraine induced nausea and vomiting. Metoclopramide can be used in combination with oral analgesics to improve the absorption of analgesics in acute migraine.

Diagnostic procedures:
Radiology, Duodenal intubation
Metoclopramide speeds up the passage of a barium meal by increasing the rate of gastric emptying, co-ordinating peristalsis and dilating the duodenal bulb.

Metoclopramide also facilitates duodenal intubation procedures.

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

4.2 Posology and method of administration

Posology:
Adult patients
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 maximum recommended treatment duration is 5 days.
Paediatric population:
The safety and efficacy of Metoclopramide in children below 1 year has not yet been established (see section 4.3). Prevention of delayed chemotherapy induced nausea and vomiting (CINV) (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 oral route. The maximum dose in 24 hours is 0.5mg/kg body weight

Dosing table

Age	**Body weight**	**Dose**	**Frequency**
1-3 years	10-14kg	1mg	Up to 3 times a day
3-5 years	15-19kg	2mg	Up to 3 times a day
5-9 years	20-29kg	2.5mg	Up to 3 times a day
9-18 years	30-60kg	5mg	Up to 3 times a day
15-18 years	Over 60kg	10mg	Up to 3 times a day

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

Tablets are not suitable for use in children weighing less than 61 kg. Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

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).

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

Patients with 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).

Patients with Hepatic impairment:
In patients with severe hepatic impairment, the dose should be reduced by 50% (see section 5.2).
Other pharmaceutical forms/strengths may be more appropriate for administration to these populations.

Diagnostic indications:
A single dose of ' Metoclopramide ' may be given 5-10 minutes before the examination, subject to body weight consideration, (see above).

Method of administration:
For oral use only.

4.3 Contraindications

- Hypersensitivity to the active substance or to 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 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)

'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.

4.4 Special warnings and precautions for use

Precautions:
If vomiting persists the patient should be reassessed to exclude the possibility of an underlying disorder e.g. cerebral irritation.

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 antiparkinsonian 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).

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).

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.
Patients with rare hereditary problems of galactose intolerance, the total lactose deficiency of glucose-galactose malabsorption should not take this medicine.

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

Metoclopramide should not be used in the immediate postoperative period (up to 3-4 days) following pyloroplasty or gut anastomosis, as vigorous gastrointestinal contractions may adversely affect healing.

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

There have been very rare reports of abnormalities of cardiac conduction with intravenous metoclopramide. Metoclopramide should be used with care with other drugs affecting cardiac conduction.

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.

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 coadministered with strong CYP2D6 inhibitors such as fluoxetine and paroxetine. Although the clinical significance is uncertain, patients should be monitored for adverse reactions. ' Metoclopramide ' may reduce plasma concentrations of atovaquone.

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 new born 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 low level. 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 has moderate influence on the ability to drive and use machines. Metoclopramide may cause side effects including 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 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
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 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
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

* 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 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, 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 antiparkinsonian 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

ATC Code: A03FA01 (Drugs For Functional Gastrointestinal Disorders-Propulsives)

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. 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

Metoclopramide is metabolised in the liver and the predominant route of elimination of metoclopramide and its metabolites is via the kidney.

Renal impairment

The clearance of metoclopramide is reduced by up to 70% in patients with severe renal impairment, while the plasma elimination halflife 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

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Povidone
Colloidal Silicon Dioxide
Industrial methylated spirits
Magnesium Stearate

6.2 Incompatibilities

None stated.

6.3 Shelf life

24 months (blister packs).

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Tablets are packed in blister of 28's (Top foil: 212mm x 0.020mm printer aluminium

foil and base film 216mm x 0.25mm clear PVC with 60gsm PVDC).

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Relonchem Limited
Cheshire House
Gorsey Lane
Widnes
WA8 0RP

8 MARKETING AUTHORISATION NUMBER(S)

PL 20395/0131

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/07/2001

10 DATE OF REVISION OF THE TEXT

10/02/2021