Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metoclopramide hydrochloride 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains
Metoclopramide Hydrochloride equivalent to 10 mg anhydrous Metoclopramide Hydrochloride

Excipient(s) with known effect
Each tablet contains 101.24 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White to off-white, round, biconvex tablets with the inscription 'BD' on one side and a scoreline on the other side.

The tablet can be divided into equal halves.

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.

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 population

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.

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 0.5 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 5 days for prevention of delayed chemotherapy induced nausea and vomiting (CINV).
Tablets are not suitable for use in children weighing less than 30 kg.
Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

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 6.1.
- Gastrointestinal haemorrhage, mechanical obstruction or gastrointestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk.
- A history of neuroleptic or metoclopramide-induced tardive dyskinesia.
- Epilepsy (increased crises frequency and intensity)
- Parkinson's disease
- Confirmed or suspected phaeochromocytoma due to the risk of severe hypertension episodes.
- 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

Special warnings

Neurological Disorders
Extrapyramidal disorders may occur, particular 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 must 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).

Excipient warning
Metoclopramide Hydrochloride tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicine.

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 co-administered with strong CYP2D6 inhibitors such as fluoxetine and paroxetine. Although the clinical significance is uncertain, patients should be monitored for adverse reactions.

Rifampicin
In a published study in 12 healthy volunteers, administration of rifampicin 600 mg for 6 days decreased metoclopramide plasma exposure (AUC) and maximum concentration (Cmax) by 68% and 35, respectively.

Although the clinical significance is uncertain, when metoclopramide is combined with rifampicin or other potent inducers (eg, carbamazepine, phenobarbital, phenytoin), patients should be monitored for any lack of antiemetic effect.

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 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 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 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 (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions
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 4.4); atrioventricular block, sinus arrest particularly with intravenous formulations; 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	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	Convulsions 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 thoughts
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 with hyperprolactinaemia (amenorrhoea, galactorrhoea, gynaecomastia).

[$]Patients with poor CYP2D6 metabolization may be at increased risk of extrapyramidal disorders (see section 5.2).

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: preparations to combat nausea/vomiting.
ATC code: A03F A01

Metoclopramide is a substituted benzamide. It is used among other things because of its anti-emetic properties. The anti-emetic effect is the result of two mechanisms of action involving the central nervous system:

- antagonism of the dopaminergic D2 receptors in the chemoreceptor trigger zone and in the vomiting centre of the medulla which is affected in apomorphine-induced vomiting;
- antagonism of the serotoninergic 5HT3 receptors and agonist effect on the 5HT4 receptors which are affected in chemotherapy-induced vomiting.

In addition to the central action, metoclopramide has a stimulant effect on gastrointestinal motility via a peripheral mechanism of action. There is an antidopaminergic effect and potentiation of the effect of acetylcholine. This causes accelerated emptying of the stomach and there is an increase in the pressure exerted by the lower oesophageal sphincter. Metoclopramide has no effect on gastric secretions.

5.2 Pharmacokinetic properties

Following oral administration the relative bioavailability compared with intravenous administration is 60 to 100%. Peak plasma concentrations are reached within 0.5 to 2 hours.

The distribution volume is 2-3 l/kg; 13-22% is bound to plasma proteins. Metoclopramide is excreted primarily in the urine, both in unchanged form and in sulfate or glucuronide conjugate form. The principal metabolite is an N-4 sulphur conjugate.

The plasma elimination half-life is 5 to 6 hours, irrespective of the route of administration.

Special patient populations

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.

CYP2D6 poor metabolizers
Metoclopramide elimination may be slower in patients who are CYP2D6 poor metabolisers (compared to patients who are CYP2D6 intermediate, extensive or ultra-rapid metabolisers); possibly increasing the risk of extrapyramidal disorders to metoclopramide (see section 4.8).

5.3 Preclinical safety data

No abnormalities have been found in animal studies to indicate a safety risk in humans. This is based on data from pharmacological studies relating to safety, and data on toxicity following repeated administration, genotoxicity, carcinogenicity and reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablet contains the following excipients:
Lactose monohydrate.
Pre-gelatinised starch.
Maize starch.
Anhydrous colloidal silica.
Magnesium stearate.

6.2 Incompatibilities

No particulars.

6.3 Shelf life

The shelf life is 2 years in PVC/PVdC/aluminium blister strips.

6.4 Special precautions for storage

Store below 30 ºC.

6.5 Nature and contents of container

Metoclopramide Hydrochloride tablets are packaged in PVC/PVdC/aluminium blister strips. The carton contains 20, 24, 28, 30, 40, 50, 60, 84, 100, 500 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/204/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th March 2016
Date of last renewal: 31st December 2015

10 DATE OF REVISION OF THE TEXT

September 2026