

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Metoclopramide Tablets BP 10mg

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains Metoclopramide Hydrochloride BP, equivalent to 10mg Anhydrous Metoclopramide Hydrochloride.

Excipient(s) with known effect

The tablets contain lactose.

For a full list of excipients see section 6.1

### **3 PHARMACEUTICAL FORM**

Uncoated tablet

White, biconvex tablets embossed M/10 on one face and 'PV' on the other.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

##### **Adult Population**

Metoclopramide tablets are 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 of oral analgesics to improve the absorption of analgesics in acute migraine.

##### **Paediatric population**

Metoclopramide tablets are 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

Adult Patients (all indications):

The recommended single dose is 10mg 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	10-14 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).

Metoclopramide 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.

### Special Population

#### Elderly patients:

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  $\leq$  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).

Other pharmaceutical forms/strengths may be more appropriate for administration to these populations.

**Method of administration:**

For oral 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).
- Metoclopramide should not be used during 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 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 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.

### **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. 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.

**Contains Lactose:**

Patients with rare hereditary problems of galactose intolerance, total lactose deficiency or 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 post-operative period (up to 3 – 4 days) following pyloroplasty or gut anastomosis, as vigorous gastrointestinal contraction may adversely affect healing.

Special care should be taken when administering Metoclopramide intravenously to patient 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 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 (C<sub>max</sub> 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.

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 neither 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 Effect 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
<b>Blood and lymphatic system disorders</b>		
	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.
<b>Cardiac Disorders</b>		
	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;
<b>Endocrine disorders*</b>		
	Uncommon	Amenorrhoea, Hyperprolactinaemia
	Rare	Galactorrhoea
	Not known	Gynaecomastia
<b>Gastrointestinal disorders</b>		
	Common	Diarrhoea
<b>General disorders and administration site conditions</b>		
	Common	Asthenia
<b>Immune system disorders</b>		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock particularly with intravenous formulation).
<b>Nervous system disorders</b>		
	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, 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).
<b>Psychiatric disorders</b>		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional state
<b>Vascular disorder</b>		
	Common	Hypotension, particularly with intravenous formulation
	Not known	Shock, syncope after injectable us, 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](http://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 levels 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**

ATC Code: A03F A01 (Antispasmodic and anticholinergic agents and propulsives).

Metoclopramide hydrochloride is a substituted benzamide which stimulates the motility of the upper gastro-intestinal tract without affecting gastric acid secretion.

Metoclopramide hydrochloride increases gastric peristalsis leading to accelerated gastric emptying. Duodenal peristalsis is also increased which decreases intestinal transit time. The resting tone of the gastro-oesophageal sphincter is increased and the pyloric sphincter is relaxed.

Metoclopramide possesses parasympathomimetic activity as well as being a dopamine receptor antagonist with a direct effect on the Chemoreceptor trigger zone. Metoclopramide also increases prolactin secretion.

### **5.2 Pharmacokinetics Properties**

#### **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**

N/A

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients:**

Lactose  
Maize starch  
Magnesium stearate  
Colloidal silicon dioxide  
Sodium starch glycollate

**6.2. Incompatibilities**

None known.

**6.3. Shelf life**

5 years

**6.4 Special precautions for storage:**

Store in a dry cool condition protected from bright sunlight.

**6.5 Nature and contents of container**

Plastic securitainer with polypropylene lids with double security closure  
Containing Metoclopramide tablets (material of the container complies to EEC directives for plastic in contact with drugs and food stuffs), in pack size of 28, 50, 56, 100, 200, 500 and 1000's

Blister packs of 0.25mm thick PVC and Aluminium foil of thickness 20 Microns  
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal:**

None

**7. MARKETING AUTHORISATION HOLDER**

Pharmvit Limited  
177, Bilton Road,  
Perivale, Greenford,  
Middlesex UB6 7HQ.

**8. MARKETING AUTHORISATION NUMBER:**

PL 04556/0007

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation 26<sup>th</sup> March 1984

Date of renewal 30<sup>th</sup> July 2008

**10 DATE OF REVISION OF THE TEXT**

12/04/2019