Professional Information for BIO-METOCLOPRAMIDE

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

BIO-METOCLOPRAMIDE 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains metoclopramide monohydrochloride monohydrate equivalent to 10 mg metoclopramide monohydrochloride.

Excipients with known effects:

Contains sugar (101,24 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White biconvex tablets, with break-line on one side, plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Digestive disorders:

BIO-METOCLOPRAMIDE is indicated in conditions associated with gastric stasis or hypomotility.

Anti-emetic use:

BIO-METOCLOPRAMIDE is used in the control of nausea in the following conditions: medicine-induced vomiting and gastrointestinal disorders.

4.2 Posology and method of administration

Posology

Adults:

One tablet three times daily.

Children:

(5 to 14 years)

Half a tablet three times daily.

The total daily dose in children and young adults should not exceed 0,5 mg/kg body mass.

Method of administration

For oral use only.

4.3 Contraindications

- Hypersensitivity to metoclopramide monohydrochloride 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. BIO-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 (see section 4.4).
- Patients with suspected or confirmed phaeochromocytoma, because BIO-METOCLOPRAMIDE may cause a hypertensive crisis (see section 4.4).
- Pregnancy and lactation (see section 4.6 and section 4.4).
- History of neuroleptic or metoclopramide-induced tardive dyskinesia.
- Epilepsy (increased crises frequency and intensity).
- Parkinson's disease.
- Porphyria.
- Combination with levodopa or dopaminergic agonists (see section 4.5).
- Combination with phenothiazine treatment (see section 4.5).

- Known history of methaemoglobinaemia with metoclopramide or of nicotinamide adenine dinucleotide (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

The use of metoclopramide during pregnancy is considered unsafe as teratogenicity has been demonstrated in animal studies (see section 4.3).

A time interval of at least 6 hours should be respected between each BIO-METOCLOPRAMIDE dose, even in the event of vomiting and rejection of the dose, in order to avoid overdose.

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

Neurological disorders

Potentially reversable tardive dyskinesia, especially in the elderly, has been reported during prolonged therapy and long-term treatment should be regularly reviewed. 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). BIO-METOCLOPRAMIDE should be discontinued immediately in the event of symptoms of neuroleptic malignant syndrome and appropriate treatment should be initiated.

Care should be exercised when concomitant medicines that can also cause extrapyramidal side effects, such as the phenothiazines, are taken (see section 4.3).

Extrapyramidal disorders may occur, particularly in children, young adults, the elderly, and/ or when high doses are used. These reactions occur usually at the beginning of the treatment and can occur

after a single administration. BIO-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 medicines in adults).

Special care should be exercised in patients with underlying neurological conditions and in patients being treated with other centrally-acting medicines (see section 4.3). The effects of central nervous system depressants may be enhanced.

Hypertension

Hypertensive crises have occurred in patients with phaeochromocytomas given BIO-METOCLOPRAMIDE (see section 4.3). BIO-METOCLOPRAMIDE should be used with caution in patients with hypertension, since there is limited evidence that BIO-METOCLOPRAMIDE may increase circulating catecholamines in such patients.

Parkinson's disease

BIO-METOCLOPRAMIDE is contraindicated in patients with parkinsonism (see section 4.3). Symptoms of Parkinson's disease may also be exacerbated by BIO-METOCLOPRAMIDE.

Methaemoglobinaemia

Methaemoglobinaemia which could be related to NADH cytochrome-b5 reductase deficiency has been reported. In such cases, BIO-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 (see section 4.8). Special care should be taken BIO-METOCLOPRAMIDE to the

elderly population, patients with cardiac conduction disturbances (including QT prolongation), patients with uncorrected electrolyte imbalance, bradycardia and those taking other medicines known to prolong QT interval.

Renal and hepatic impairment

In patients with renal impairment or with severe hepatic impairment, a dose reduction is recommended.

Reproductive system

BIO-METOCLOPRAMIDE may cause elevation of serum prolactin levels (see section 4.5).

Atopy and porphyria

Care should be exercised when using BIO-METOCLOPRAMIDE in patients with a history of atopy (including asthma) or porphyria (see section 4.3).

Post-operative

BIO-METOCLOPRAMIDE should not be used in the immediate post-operative period (up to 3 to 4 days) following pyloroplasty or gut anastomosis, as vigorous gastrointestinal contractions may adversely affect healing (see section 4.3).

Chronic administration

An increase in mammary neoplasms has been found in rodents after chronic administration of metoclopramide.

Paediatric population

BIO-METOCLOPRAMIDE should be used with care in children and young patients, since they are at an increased risk of extrapyramidal reactions usually at the beginning of the treatment and can occur after a single administration. BIO-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).

Lactose monohydrate

BIO-METOCLOPRAMIDE contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take BIO-METOCLOPRAMIDE.

4.5 Interaction with other medicines and other forms of interaction

Anticholinergic medicines antagonise the effects of BIO-METOCLOPRAMIDE; narcotic analgesics may act similarly.

Contraindicated combinations (see section 4.3)

Levodopa or dopaminergic agonists and metoclopramide, as in BIO-METOCLOPRAMIDE, have a mutual antagonism.

Phenothiazine coadministration increases the risk for extrapyramidal reactions.

Combinations to be avoided

Alcohol potentiates the sedative effect of BIO-METOCLOPRAMIDE.

Combinations to be taken into account

Due to the prokinetic effect of BIO-METOCLOPRAMIDE, the absorption of certain medicines may be modified.

Anticholinergics and morphine derivatives

Anticholinergics and morphine derivatives may have both a mutual antagonism with BIO-METOCLOPRAMIDE on digestive tract motility.

Central nervous system (CNS) depressants (morphine derivatives, anxiolytics, sedative H_1 antihistamines, sedative antidepressants, barbiturates, clonidine and related)

Sedative effects of CNS depressants and BIO-METOCLOPRAMIDE are potentiated.

Neuroleptics

BIO-METOCLOPRAMIDE may have an additive effect with other neuroleptics on the occurrence of extrapyramidal disorders.

Serotonergic medicines

The use of BIO-METOCLOPRAMIDE with serotonergic medicines such as SSRIs may increase the risk of serotonin syndrome.

Digoxin

BIO-METOCLOPRAMIDE may decrease digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.

Ciclosporin

BIO-METOCLOPRAMIDE increases ciclosporin bioavailability (C_{max} by 46 % and exposure by 22 %). Careful monitoring of ciclosporin plasma concentration is required. The clinical consequence is unknown.

Mivacurium and suxamethonium

Metoclopramide injection may prolong the duration of neuromuscular block (through inhibition of plasma cholinesterase).

Strong CYP2D6 inhibitors

BIO-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 medicines with potential central stimulant effects, e.g. monoamine oxidase inhibitors (MAOIs) and sympathomimetics, may be modified when prescribed with BIO-METOCLOPRAMIDE and their dosage may need to be adjusted accordingly.

Aspirin, paracetamol

BIO-METOCLOPRAMIDE may affect the adsorption of other medicines by either diminishing absorption from the stomach or by enhancing absorption from the small intestine (e.g. the effects of paracetamol and aspirin are enhanced).

Atovaquone

BIO-METOCLOPRAMIDE may reduce plasma concentrations of atovaquone.

Lithium

Increased toxicity may occur in patients receiving lithium.

Hyperprolactinaemic medicines

BIO-METOCLOPRAMIDE may also increase prolactin blood concentrations and therefore interfere with medicines which have a hypoprolactinaemic effect e.g. bromocriptine (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and/ or efficacy have not been established (see section 4.3 and section 4.4).

Breastfeeding

Metoclopramide is excreted in breast milk at low levels and adverse reactions in the breastfed baby

cannot be excluded.

BIO-METOCLOPRAMIDE is not recommended during breastfeeding (see section 4.3).

Fertility

No fertility data available.

4.7 Effects on ability to drive and use machines

BIO-METOCLOPRAMIDE may cause drowsiness, dizziness, dyskinesia and dystonia which may affect vision and interfere with the ability to drive and operate machinery.

Caution is advised when driving a vehicle or operating machinery until the effects of BIO-METOCLOPRAMIDE are known.

4.8 Undesirable effects

Blood and the lymphatic system disorders:

Frequency unknown: 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 medicines

Immune system disorders:

Less frequent: hypersensitivity

Frequency unknown: anaphylactic reaction (including anaphylactic shock)

Endocrine disorders:

Less frequent: galactorrhoea, amenorrhoea, hyperprolactinaemia

Frequency unknown: gynaecomastia, transient increases in plasma aldosterone concentrations

Psychiatric disorders:

Frequent: depression

Less frequent: hallucination, confusional state

Frequency unknown: anxiety, insomnia

Nervous system disorders:

Frequent: drowsiness, dizziness, headache, somnolence, extrapyramidal disorders which may include feelings of restlessness, involuntary movements of limbs and facial grimacing, torticollis, rhythmic protrusion of tongue, bulbar type of speech, trismus or an unnatural positioning of the head and shoulders (particularly in children and young adults and/or when the recommended dose is exceeded, even following administration of a single dose of the medicine) (see section 4.4), parkinsonism, akathisia. There may be a general increase in muscle tone. These are common in young patients especially if female.

Less frequent: dystonic reactions resembling tetanus (including visual disturbances and oculogyric crisis), dyskinesia, depressed level of consciousness, convulsion especially in epileptic patients

Frequency unknown: 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)

Cardiac disorders:

Less frequent: bradycardia

Frequency unknown: atrioventricular block, electrocardiogram QT prolonged, torsades de pointes

Vascular disorders:

Frequent: hypotension

Frequency unknown: shock, hypertensive crises in patients with phaeochromocytoma (see section 4.3), transient increase in blood pressure

Gastrointestinal disorders:

Frequent: diarrhoea, constipation

Frequency unknown: nausea, bowel upsets

Skin and subcutaneous tissue disorders:

Frequency unknown: oedema of tongue, periorbital oedema, skin rashes, pruritus, angioedema, urticaria

Renal and urinary disorders:

Frequency unknown: urinary incontinence

Reproductive system and breast disorders:

Less frequent: breast engorgement, impotence

General disorders and administration site conditions:

Frequent: asthenia

Frequency unknown: lassitude, fatigue

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BIO-METOCLOPRAMIDE is important. It allows continued monitoring of the benefit/risk balance of BIO-METOCLOPRAMIDE. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

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 anti-parkinsonian medicines in adults).

Emetics should not be used.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.7.2 Anti-emetics and antivertigo preparations

Pharmacotherapeutic group: Propulsives, agents stimulating gastrointestinal motility

ATC code: A03FA01

BIO-METOCLOPRAMIDE acts peripherally to enhance the action of acetylcholine at the muscarinic synapses, thereby increasing the motility and tone of the stomach and intestine, relaxing the sphincters and stimulating gastric secretion. It also acts centrally by antagonising dopamine.

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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicone dioxide

Lactose monohydrate

Magnesium stearate

Maize starch.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Securitainers containing 10, 100 and 500 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground floor, Block K West, Central park

400 16th Road, Randjespark

Halfway House

Midrand 1685

8. REGISTRATION NUMBER

V/5.7.2/352

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 November 1988

10. DATE OF REVISION OF THE TEXT

05 February 2024