BIODEAL LABORATORIES LIMITED
NAIROBI, KENYA

1.5.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCT CHARACTERISTICS)

APPLICATION DOSSIER FOR REGISTRATION OF EMETON SYRUP

SUMMARY OF PRODUCT CHARACTRISTICS

1. Name of the medicinal product

Emeton Syrup

2. Qualitative and quantitative composition

Each 5 ml contains Metoclopramide hydrochloride.5.0mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Syrup

Homogeneous, clear, orange colored syrup free from any visible impurities.

4. Clinical particulars

4.1 Therapeutic indications

Adult population

Metoclopramide oral solution 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 oral solution is indicated in children (aged 1 to 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 0.5 mg/kg body weight.

Paediatric population

Metoclopramide is contraindicated in children aged less than 1 year (see section 4.3).

The recommended single dose is 0.1 to 0.15 mg/kg body weight, repeated up to three times daily. 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	
5-9 years	20-29 kg	2.5 mg	
9-18 years	30-60 kg	5 mg	
15-18 years	over 60 kg	10 mg	

Elderly patients

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 to 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).

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).

Duration of administration

The maximum recommended treatment duration is 5 days.

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 reductase deficiency

- Prolactin-dependent tumor

- 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

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).

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).

This medicinal product contains methyl-parahydroxybenzoate and propyl-parahydroxybenzoate and may therefore cause allergic reactions (possibly delayed).

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, e.g.: oral contraceptives (additional contraceptive measures are recommended) cimetidine, paracetamol, various antibiotics and lithium.

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_{max} 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.

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 with other neuroleptics), in case of metoclopramide administration at the end of pregnancy, extrapyramidal syndrome in newborns cannot be excluded. Metoclopramide should be avoided at the end of pregnancy. If metoclopramide is used, neonatal monitoring should be undertaken.

Breast-feeding

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 breast-feeding women should be considered.

Fertility

Metoclopramide caused reversible impairment of spermatogenesis in rats. The relevance of this finding to humans is unclear (see section 5.3)

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 are listed by System Organ Class. Frequencies are defined using the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (frequency 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 sulphur-releasing medicinal products
Immune system disorders	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock particularly with intravenous formulation)
*Endocrine disorders**	Uncommon	Amenorrhoea, Hyperprolactinaemia
	Rare	Galactorrhoea
	Not known	Gynaecomastia
Psychiatric disorders	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional state
	Not known	Anxiety, restlessness
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 older patients (see section 4.4), Neuroleptic malignant syndrome (see section 4.4), headache, dizziness
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, cardiac arrhythmias in association with tachycardia
Vascular disorders	*Common*	Hypotension, particularly with intravenous formulation
	Not known	Shock, Syncope after injectable use, Acute hypertension in patients with phaeochromocytoma (see section 4.3), transient rise in blood pressure
Gastrointestinal disorders	Common	Diarrhoea
General disorders and administration site conditions	Common	Asthenia

* Endocrine disorders during prolonged treatment in relation with hyperprolactinemia (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, and hallucination.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 https://www.tmda.go.tz/pages/electronic-submission-of-adverse-drug-reactions.

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: Drugs for functional gastrointestinal disorders, Propulsives ATC code: A03FA01

Pharmacodynamic effects

Metoclopramide hydrochloride is a central dopamine D_2 receptor antagonist with additional cholinergic activity. There are 2 main effects:

1. Antiemetic efficacy,

2. Accelerated gastric emptying and small intestine transit time.

Further, metoclopramide hydrochloride works as a 5-HT_3 receptor antagonist and a 5-HT_4 receptor agonist.

The antiemetic effect is probably based upon an inhibition of dopaminergic neurons leading to an increased sensitivity threshold in the chemoreceptor's trigger zone of the brain stem. The increased motility of the gastrointestinal tract is controlled both by superordinate centres of the brain and peripheral stimulation of neuronal postganglionic cholinergic receptors. The inhibition of dopaminergic receptors of stomach and intestine may possibly play a part.

Undesirable effects are mainly extrapyramidal symptoms (involuntary convulsions) caused by the dopamine-receptor blocking effect of metoclopramide hydrochloride in the CNS.

Prolonged use may lead to an increase in the prolactin concentration in serum due to the failure of the dopaminergic inhibition of the prolactin secretion. Galactorrhoea and disorders of the menstrual cycle in women and gynaecomastia in men have been described; they resolve after stopping the medication.

5.2 Pharmacokinetic properties

Absorption

Metoclopramide hydrochloride is rapidly absorbed after oral administration. Peak plasma concentrations of metoclopramide occur about 30 to 120 min, on average 60 min, after an oral dose. Bioavailability of oral metoclopramide hydrochloride is 60 to 80% on average.

After oral administration of 10 mg metoclopramide hydrochloride (immediate release) peak plasma concentrations of 42 to 63 ng/ml were determined in six subjects. Peak plasma concentrations after oral dosing may differ widely. This may be due to the interindividually variable first-pass metabolism of metoclopramide hydrochloride.

Distribution

The volume of distribution of metoclopramide hydrochloride is between 2.2 and 3.4 l/kg.

It is weakly bound to plasma proteins.

Metoclopramide crosses the blood-brain barrier.

Metoclopramide crosses the placenta and is excreted into breast milk.

Biotransformation

Within 24 h, 78% of radioactively labeled metoclopramide hydrochloride appear in human urine as unchanged metoclopramide hydrochloride, conjugated (as sulfate or glucuronide conjugates), and as 2-(2-methoxy-4-amino-5-chlorine-benzoyl)-amino-acetic acid.

Elimination

In humans the main route of excretion of metoclopramide hydrochloride and its metabolites is via the kidneys. The elimination half-life is between 2.6 and 4.6 h depending on the pharmaceutical form. Long-term treatment does not cause accumulation of metoclopramide hydrochloride.

Patients with 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 to 50 ml/minute and 15 hours for a creatinine clearance < 10 ml/minute).

Patients with 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

Acute toxicity

The acute toxicity was tested in different animal species (mouse, rat, and dog). The toxicity symptoms shown are the same as stated in section 4.9.

Chronic toxicity / sub chronic toxicity

Subchronic and chronic application of oral and intravenous doses showed corresponding toxicity descriptions in all animals: in dogs and rabbits less food intake, reduced increase of body weight development, diarrhoea, leukocytes and anaemia, increase of LDH and AP, sedation, anorexia; in rats increase of SGOT, SGPT and of total bilirubin.

The lowest toxic dose lay, after chronic application to rat and dog, between 11-35 mg/kg; the lethal dose range can be expected between 35-115 mg/kg per os. The lowest toxic dose in the dog lay between 6-18 mg/kg IV, in rabbit between 2-10 mg/kg IV.

Mutagenic and tumourigenic potentials

Metoclopramide was not subjected to a comprehensive study on mutagenicity. Mutagenicity studies on three bacterial strains (salmonella) produced no evidence of mutagenic properties.

A study over 77 weeks on the tumourigenic potential in rats with oral doses, which lay 40 times higher than the therapeutical dose in humans, produced no further particularities than an increase of the serum prolactin level. Further, neither in clinical nor in epidemiological studies a correlation between the chronic use of prolactin-stimulating substances and mamma tumourigenesis could be found.

Reproductive toxicology

Studies on reproduction were conducted in three animal species (mouse, rat, rabbit). Up to the highest tested dosage range (116.2 resp. 200 mg/kg orally) no signs of a teratogenic or embryotoxic effect could be found.

Dosages, which led to an increase of the prolactin level, caused reversible spermatogenetic disorders in rats.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Benzoate B.P

Sodium Saccharin B.P.

Cello cell B.P.

Citric Acid B.P.

Tatrazine Yellow Colour

Ponceau 4R Colour

Raspberry Flavour

Pineapple Flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Stability after first opening: 6 months.

6.4 Special precautions for storage

Keep the bottle in the outer carton.

Storage after first opening: Do not store above 30°C.

6.5 Nature and contents of container

60 ml amber coloured (Glass/PET) bottles, 25 mm Aluminium caps, Emeton Syrup 60ml unit boxes, Emeton Syrup Literatures, Emeton Syrup 60ml labels, 150 x 60ml Shippers, and Brown Bopp tape

6.6 Special precautions for disposal and other handling

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

7. Marketing authorization holder

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8. Marketing authorization number(s)

H2018/CTD2172/478ER

9. Date of first authorization/renewal of the authorization

27/06/ 2019

10. Date of revision of the text

20.09.2022